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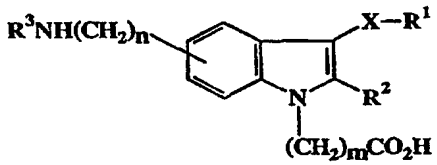
(54) Title: INDOLE DERIVATIVES THROMBOXANE A2 ANTAGONISTS



(I)

(57) Abstract

Compounds of formula (I) and pharmaceutically acceptable salts and biolabile esters thereof, wherein R^1 is H, C_1-C_4 alkyl, phenyl optionally substituted by up to three substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and CF_3, or is 1-imidazolyl, 3-pyridyl or 4-pyridyl, R^2 is H or C_1-C_4 alkyl, R^3 is SO_2R^4 or COR^4 where R^4 is C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl$(CH_2)_p$, C_3-C_6 cycloalkyl$(CH_2)_p$, aryl$(CH_2)_p$ or heteroaryl$(CH_2)_p$, p being 0, 1 or 2, or R^4 may be NR^5R^6 where R^5 is H or C_1-C_4 alkyl and R^6 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or aryl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a 5- to 7-membered heterocyclic ring which may optionally incorporate a carbon-carbon double bond or a further heteroatom linkage selected from O, S, NH, N(C_1-C_4 alkyl) and N(C_1-C_5 alkanoyl); X is CH_2 or a direct link, with the proviso that when R^1 is 1-imidazolyl then X is CH_2; m is 2, or 3; n is 0, 1 or 2 and wherein the group $(CH_2)_nNHR^3$ is attached at the 5-position when n is 0 or 1, or at the 5- or 4-position when n is 2. These compounds are selective TXA_2 and PGH_2 antagonists. Some also inhibit thromboxane synthetase.

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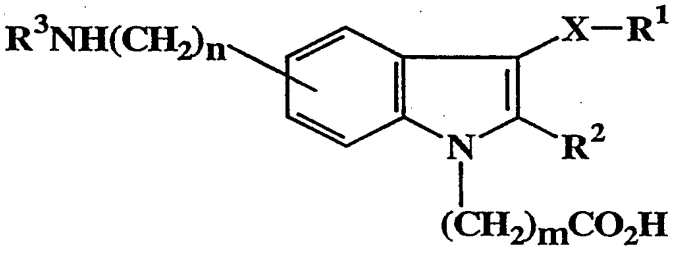
Indole derivatives thromboxane A2 antagonists

This invention relates to certain indole alkanoic acids. Such compounds are able to selectively antagonise the effect of thromboxane A_2 (TXA_2), and its precursor prostaglandin H_2 (PGH_2), at the thromboxane receptor. In addition, certain of the compounds also selectively inhibit the thromboxane synthetase enzyme. The compounds are thus useful as therapeutic agents and they may be used either alone, or, in the case of compounds which do not inhibit the thromboxane synthetase enzyme, preferably in combination with a thromboxane synthetase inhibitor, for example in the treatment of atherosclerosis and unstable angina and for prevention of reocculsion, both acute and chronic, after percutaneous transluminal coronary and femoral angioplasty. The compounds may also find clinical utility in a further variety of disease conditions in which thromboxane A_2 has been implicated such as in the treatment of myocardial infarction, stroke, cardiac arrhythmias, transient ischaemic attack, tumour metastasis, peripheral vascular disease, bronchial asthma, renal disease, cyclosporin-induced neprotoxicity, renal allograft rejection, vascular complications of diabetes and endotoxin shock, trauma, pre-eclampsia and in coronary artery bypass surgery and haemodialysis.

The compounds of the invention are of formula (I):



(I)

and pharmaceutically acceptable salts and biolabile esters thereof,

wherein R^1 is H, C_1-C_4 alkyl, phenyl optionally substituted by up to three substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and CF_3, or is 1-imidazolyl, 3-pyridyl or 4-pyridyl,

R^2 is H or C_1-C_4 alkyl,

R^3 is SO_2R^4 or COR^4 where R^4 is C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl$(CH_2)_p$, C_3-C_6 cycloalkyl$(CH_2)_p$, aryl$(CH_2)_p$ or heteroaryl$(CH_2)_p$, p being 0, 1 or 2, or R^4 may be NR^5R^6 where R^5 is H or C_1-C_4 alkyl and R^6 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or aryl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a 5- to 7-membered heterocyclic ring which may optionally incorporate a carbon-carbon double bond or a further heteroatom linkage selected from O, S, NH, N(C_1-C_4 alkyl) and N(C_1-C_5 alkanoyl);

X is CH_2 or a direct link, with the proviso that when R^1 is 1-imidazolyl then X is CH_2;

m is 2, or 3

n is 0, 1 or 2

and wherein the group $(CH_2)_nNHR^3$ is attached at the 5-position when n is 0 or 1, or at the 5- or 4-position when n is 2.

In the above definitions "aryl" means phenyl or naphthyl and "heteroaryl" means furyl, thienyl or pyridyl, any of which ring systems may optionally be substituted with one to three substituents each independently chosen from C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, OCF_3 and CN. Alkyl and alkoxy groups having three or more carbon atoms may be straight chain or branched chain. "Halo" means fluoro, chloro, bromo or iodo.

Compounds containing asymmetric centres can exist as enantiomers and diastereisomers, and the invention includes the separated individual isomers as well as mixtures of isomers.

Also included in the invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

The term biolabile ester in the above definition means a pharmaceutically acceptable, biologically degradable ester derivative of a compound of formula (I), that is a prodrug which, upon administration to an animal or human being, is converted in the body to a compound of formula (I). In the case of the compounds of formula (I), such biolabile ester prodrugs are particularly advantageous in providing compounds of formula (I) suitable for oral administration. The suitability of any particular ester-forming group can be assessed by conventional in vivo animal or in vitro enzyme hydrolysis studies. Thus desirably, for optimum effect, the ester should only be hydrolysed after absorption is complete. Accordingly, the ester should be resistant to premature hydrolysis by digestive enzymes before absorption, but should be productively hydrolysed by, for example, gut-wall, plasma or liver enzymes. In this way, the active acid is released into the bloodstream following oral absorption of the prodrug.

Suitable biolabile esters may include alkyl, alkanoyloxyalkyl, cycloalkanoyloxyalkyl, aroyloxyalkyl and alkoxycarbonyloxyalkyl esters, including cycloalkyl and aryl substituted derivatives thereof, aryl esters and cycloalkyl esters, wherein said alkyl, alkanoyl or alkoxy groups may contain from 1 to 8 carbon atoms and be branched-chain or straight-chain, said cycloalkyl groups may contain from 3-7 carbon atoms and said cycloalkyl groups may contain from 3-7 carbon atoms wherein both are optionally benzo-fused, and said aryl and aroyl groups include substituted phenyl, naphthyl or indanyl ring systems. Preferably, the biolabile esters of the invention are C_1-C_4 alkyl esters. More preferably, they are methyl, ethyl and t-butyl esters.

The pharmaceutically acceptable salts of the compounds of formula (I) are those formed with bases which provide non-toxic salts. Examples include the alkali and alkaline earth metal salts such as the sodium potassium or calcium salts, and salts with amines such as diethylamine.

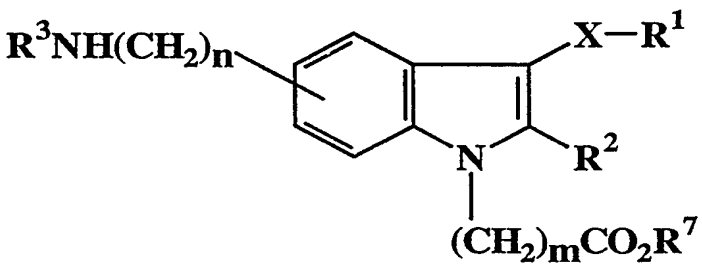
A preferred group of compounds of formula (I) is that where R^1 is optionally substituted phenyl or pyridyl, R^2 is H, R^3 is SO_2R^4 where R^4 is optionally substituted phenyl, X is CH_2, m is 2, n is 0 or 2, and $(CH_2)_nNHR^3$ is attached at the 5-position.

Another preferred group of compounds of formula (I) is that where R^1 is pyridyl, R^2 is H, R^3 is SO_2R^4 where R^4 is optionally substituted phenyl or, R^3 is COR^4 where R^4 is alkyl, X is CH_2, m is 2, n is 2 and $(CH_2)_nNHR^3$ is attached at the 4-position.

Particularly preferred are such compounds wherein R^1 is 4-fluorophenyl, R^2 is H, R^3 is 4-arylsulphonyl, X is CH_2, m is 2, n is 0 and $(CH_2)_nNHR^3$ is attached at the 5-position, or wherein R^1 is pyridyl, R^2 is H, R^3 is 3-methylbutanoyl, X is CH_2, m is 2, n is 2 and $(CH_2)_nNHR^3$ is attached at the 4-position.

In another aspect the present invention provides processes for the preparation of compounds of formula (I), their biolabile esters and pharmaceutically acceptable salts.

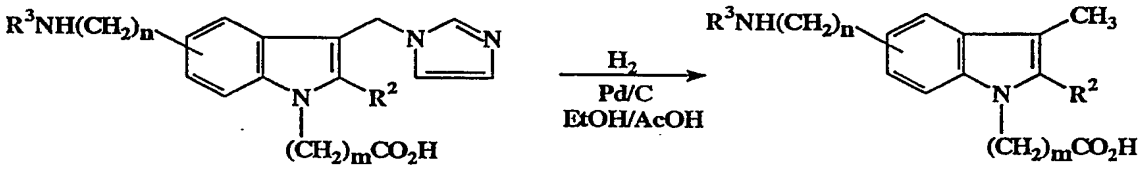
In one process, the compounds of formula (I) are obtained by hydrolysis of their lower alkyl ester precursors of formula (II):



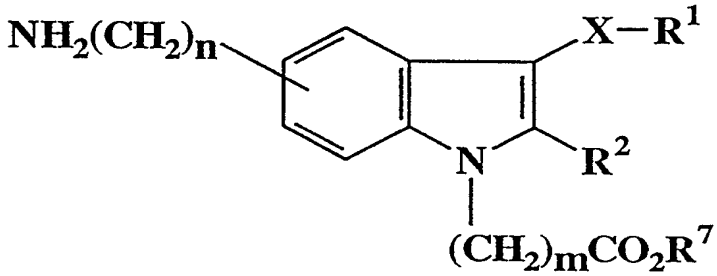
(II)

wherein R^1, R^2, R^3, m, n, p and X are as defined for formula (I) and R^7 is C_1-C_4 alkyl, preferably methyl, ethyl or t-butyl. The reaction can be conducted under basic or acidic conditions, e.g. with excess aqueous alkali, preferably sodium hydroxide solution, or excess hydrochloric acid respectively, optionally with a suitable co-solvent such as a C_1-C_4 alkanol, preferably methanol, at from ambient temperature to the reflux temperature of the reaction medium.

In the case where R^1=H and X=CH_2 (i.e. a 3-methylindole), the final compounds may be prepared by hydrogenolysis of the compound where R^1=1-imidazolyl and X=CH_2.



The compounds of formula (II) where R^3 is SO_2R^4 or COR^4 may generally be prepared by sulphonation/sulphamoylation or acylation, respectively of an amine of formula (III):



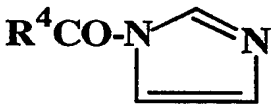
(III)

where R^1, R^2, R^7, m, n and X are as defined above. Sulphonylation may be carried out by reaction of the amine of formula (III) with a sulphonyl halide of formula R^4SO_2Hal, where Hal is a halogen atom (preferably the chloride), or with a sulphonic anhydride of formula $(R^4SO_2)O$, where R^4 is as defined above but is other than NR^5R^6. Sulphamoylation may be carried out similarly by reaction of compound (III) with a sulphamoyl halide (preferably the chloride) of formula $R^5R^6NSO_2Hal$, to yield a compound of formula (II) in which R^4 is NR^5R^6.

Acylation may be carried out by reaction of compound (III) with an acid anhydride of formula $(R^4CO)_2O$ or acid halide R^4CO Hal (preferably the chloride) where R^4 is as defined above.

These reactions may be carried out in the presence of a base such as triethylamine, pyridine, 4-dimethylaminopyridine or combination thereof to act as an acid scavenger in a suitable solvent such as methylene chloride or tetrahydrofuran.

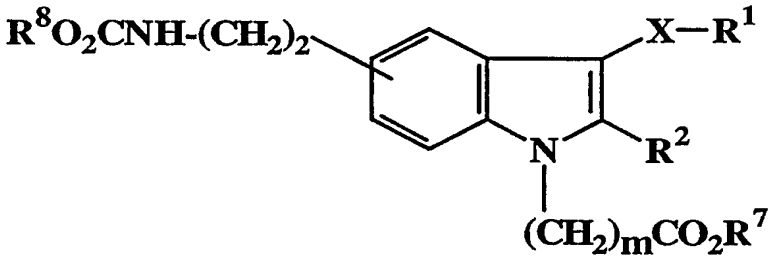
Alternatively, the acylation may be carried out by reaction of compound (III) with an imidazolide of formula



generated in situ by reaction of an acid of formula R^4CO_2H and carbonyldi-imidazole in a solvent such as tetrahydrofuran, dimethylformamide or methylene chloride.

The novel compounds of formula (II) and (III) above are themselves part of the present invention.

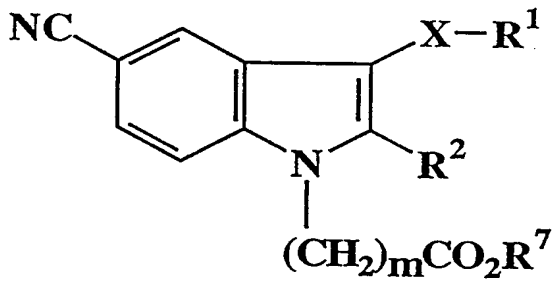
The amines of formula (III) may be prepared by different methods, depending on the value of n. When n=2 the amine may be prepared by amine deprotection from a corresponding carbamate of formula (IV):



(IV)

where R^1, R^2, R^7, m and X are as defined above and R^8 is a group which can be selectively removed in the presence of group R^7 to give the required amine. A suitable R^8 group is benzyl, which may be removed by catalytic transfer hydrogenation using ammonium formate and a palladium/ carbon catalyst in a suitable solvent such as a methanol/ tetrahydrofuran mixture at reflux temperature. Alternatively, this benzyl group may be removed by hydrogenation using hydrogen, at a pressure of 1-5 atmospheres, in the presence of a palladium/carbon catalyst and a solvent such as tetrahydrofuran, methanol or ethanol at a temperature from ambient to 50°C. Another possible R^8 is t-butyl, which may be removed by reaction with an acid such as hydrochloric or trifluoroacetic acid in a solvent such as dichloromethane at a temperature from 0 to 20°C.

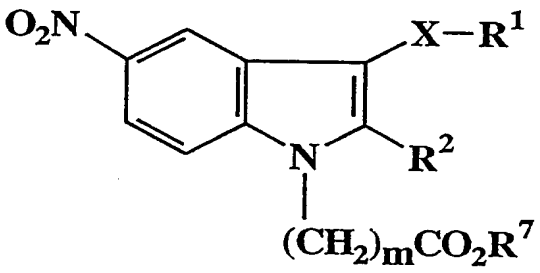
When n=1 the amine of formula (III) may be prepared by reduction of a nitrile of formula (V):



(V)

where R^1, R^2, R^7, X and m are as defined above. This reduction may be performed by hydrogenation in the presence of a metal catalyst such as rhodium/alumina, preferably in the presence of ammonia, or Raney nickel under the usual conditions for this reaction. Reduction may also be carried out by means of diborane.

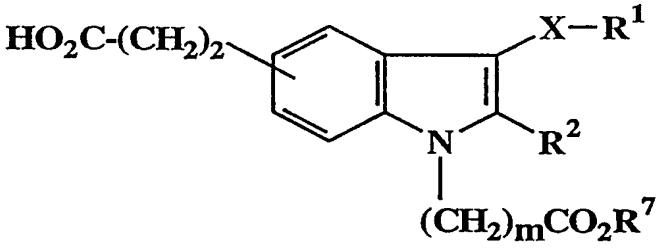
When n=0 the desired amines of formula (III) may be prepared by reduction of corresponding nitro compounds of formula (VI):



(VI)

where R^1, R^2, R^7, m and X are as defined above. This reduction may be achieved by treatment with hydrogen, typically at a pressure of 1-5 atmospheres, in a suitable solvent such as methanol or ethanol with a catalyst such as palladium/carbon at a temperature of up to 50°C.

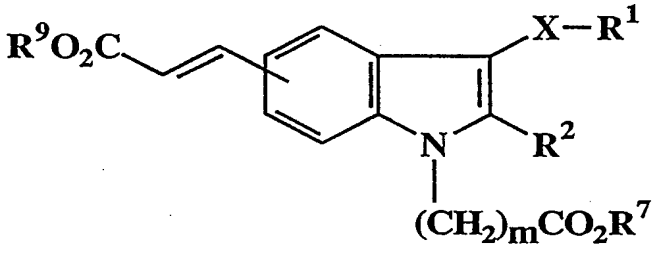
The carbamates of formula (IV) may be prepared from carboxylic acids of formula (VII):



(VII)

where R^1, R^2, R^7, X and m are as defined above by reaction with diphenylphosphoryl azide in a suitable solvent, such as dioxan, at reflux in the presence of Et_3N to form an acyl azide which undergoes the Curtius re-arrangement to give the corresponding isocyanate. Addition of an alcohol, such as benzyl or t-butyl alcohol, gives the corresponding carbamate (IV). Excess alcohol may be used as the solvent in place of dioxan.

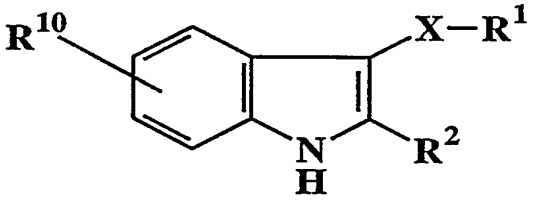
The acids of formula (VII) may themselves be prepared from acrylic esters of formula (VIII):



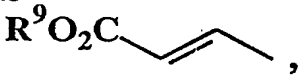
(VIII)

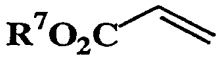
where R^1, R^2, R^7, m and X are as defined above and R^9 is a group such as benzyl or t-butyl. Catalytic transfer hydrogenation or conventional hydrogenation, as described above in relation to compounds (IV), reduces the double bond of the acrylic substituent and, when R^9 is benzyl, also removes the R^9 group to yield an acid of formula (VII). When R^9 is a group not removed by hydrogenolysis, such as t-butyl, it may be removed by treatment with a strong acid, such as hydrochloric or trifluoroacetic acid, before or after hydrogenation of the acrylic double bond.

The esters of formula (VIII), nitriles of formula (V) and nitro compounds of formula (VI) may all be prepared from indole compounds of formula (IX):

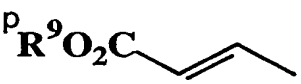


(IX)

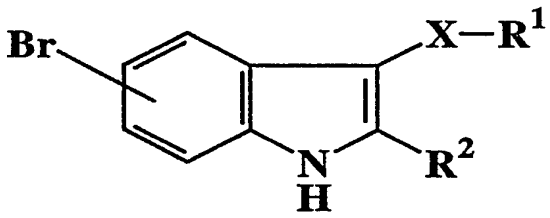
where R^1, R^2 and X are as defined above and R^{10} is  , CN or NO_2 respectively. When m=2 compound (IX) may be allowed to react with compound



in the presence of a base catalyst to give compound (VIII), (V) or (VI) by Michael addition. When m=3 these compounds may be obtained by reaction of compound (IX) with an ester of formula Hal-$(CH_2)_3$-CO_2R^7, where Hal is chloro, bromo or iodo, in the presence of a base such as sodium hydride in dimethylformamide as a solvent.

When R^{10} is the acrylic ester group 

compound (IX) may be obtained from a bromoindole of formula (X):

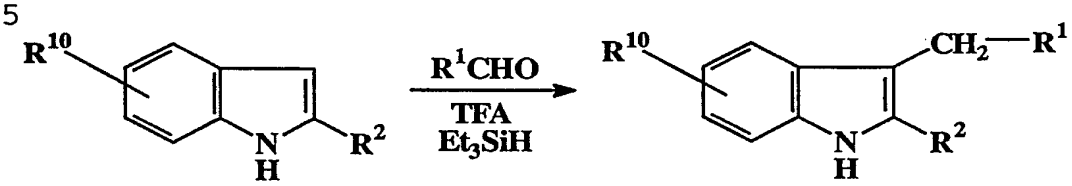


(X)

where R^1, R^2 and X are as defined above by a Heck reaction with an appropriate acrylic ester in the presence of palladium (II) acetate, tri-o-tolylphosphine and a base such as triethylamine in a suitable solvent such as acetonitrile or dimethylformamide at a temperature from 80 to 160°C.

When R^{10} is CN compound (IX) may be prepared from compound (X) by reaction of the latter with a cyanide, such as CuCN in a solvent such as dimethylformamide, dimethylacetamide or N-methylpyrrolidone at reflux temperature.

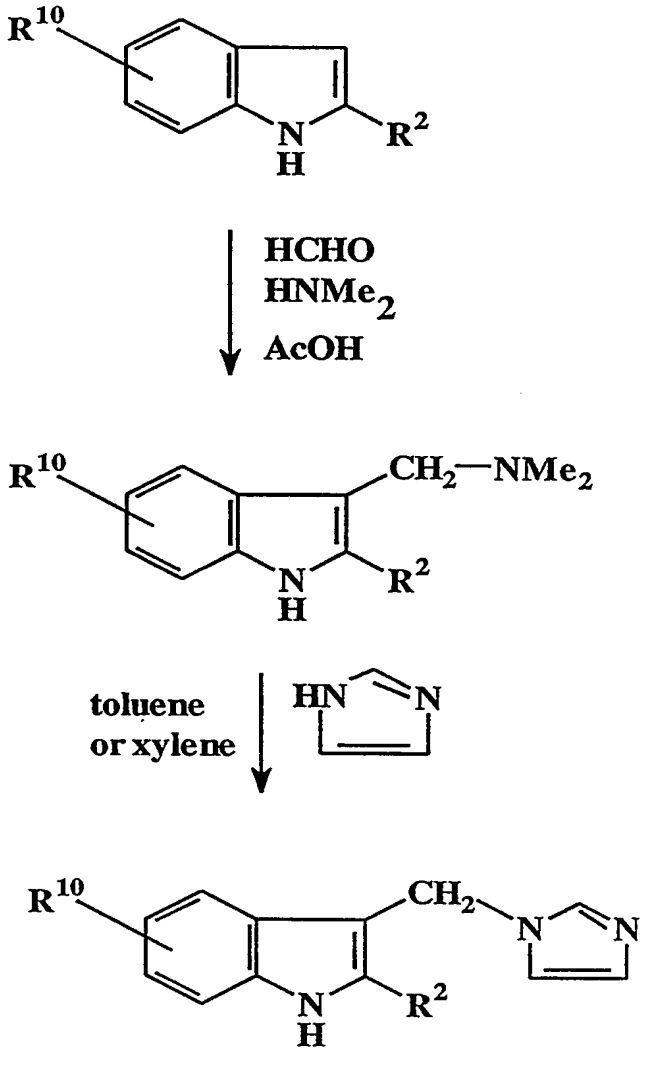
When indole intermediates in which X is CH_2, R^2 is C_1-C_4 alkyl and R^1 is not 1-imidazolyl are to be obtained, compounds (IX or X) in which X is a direct link and R^1 is H, R^2 is C_1-C_4 alkyl may be obtained by the above-described methods and subsequently allowed to react with an appropriate aldehyde in the presence of trifluoroacetic acid and triethylsilane:



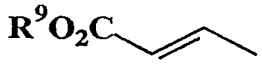
R^{10}=R^9O_2C 

NO_2 or CN or Br

When X is CH_2 and R^1 is a 1-imidazolyl group in the desired compound the following synthesis may be used:

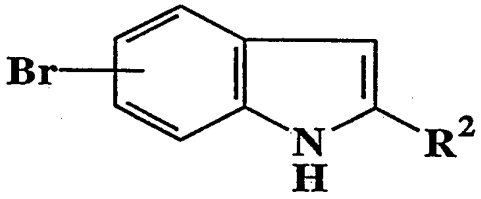


In this synthesis the starting compound in which R^2 is as defined above and R^{10} is



or CN reacts with formaldehyde, dimethylamine and acetic acid to give the corresponding indole having a $-CH_2NMe_2$ substituent at the 3-position. Subsequent treatment with imidazole in a solvent such as toluene or xylene, at the boiling point of the solvent, results in replacement of the $-NMe_2$ group with a 1-imidazolyl group.

The bromo-indole intermediates of formula (X) may be prepared from known compounds by standard methods, such as the Fischer indole synthesis or by substitution of bromocompounds (X) in which X is a direct link and R^1 is H. For example, a compound of formula (XI):



(XI)

where R^2 is as defined above may be converted to a compound (X) where X is CH_2 by reaction with aldehyde R^1CHO in the presence of trifluoroacetic acid and Et_3SiH, or with a Grignard reagent MeMgHal where Hal is a halogen atom followed by reaction with halide R^1CH_2Cl or R^1CH_2Br.

The nitroindole intermediates (IX) in which R^{10} is NO_2 may be made by known methods, such as the Fischer indole synthesis applied to the appropriate nitrophenylhydrazone. When X is CH_2 and R^1 is imidazolyl these intermediates may be prepared from those in which X is a direct link and R^1 is H by reaction with formaldehyde/dimethylamine/acetic acid followed by reaction with imidazole, as described above.

As previously mentioned, the compounds of the invention are able to antagonise the action of thromboxane A_2 and prostaglandin H_2 at the thromboxane A_2 receptor.

Thromboxane A_2 (TXA_2) is a naturally occurring prostanoid which is known to be a potent vascoconstrictor and platelet aggregating agent. TXA_2 is also believed to be involved in a number of disease states including atherosclerosis, ischaemic heart disease, peripheral vascular disease and myocardial infarction. TXA_2 acts at the thromboxane A_2 receptor, at which site other prostanoids, notably prostaglandin H_2, may also be agonists.

TXA_2 synthetase inhibitors prevent formation of TXA_2 from the precursor PGH_2 which may be diverted to produce more of the vasodilator and antiaggregatory PGI_2. However, a possible drawback with this type of agent is that accumulated PGH_2 substrate can activate the TXA_2 receptor, thus partly eliminating or negating the benefit of suppressing TXA_2 formation. Furthermore, if inhibition of TXA_2 synthetase is incomplete, sufficient TXA_2 may be available to induce some platelet activation. Both of these drawbacks can be overcome if a TXA_2 receptor antagonist is present to block the action of any TXA_2 or accumulated PGH_2 substrate. It has been demonstrated that combination of a TXA_2 antagonist and a TXA_2 synthetase inhibitor produces a synergistic effect on platelet aggregation in vitro (Watts et al., Brit. J. Pharmacol., 102, 497, 1991). In addition, administration of the TXA_2 antagonist sulotroban and the TXA_2 synthetase inhibitor dazoxiben to human volunteers gave a stronger inhibition of platelet aggregation than either agent alone (Gresele et al.,). Clin. Invest., 80, 1435, 1987).

Thus the compounds of the invention are of particular value when used in combination with a selective inhibitor of the thromboxane synthetase enzyme and the resulting combinations will find utility in the disease states already mentioned as well as those in which PGD_2 and $PGF_{2\alpha}$ may be implicated as mediators, such as diabetes, bronchial asthma, and other inflammatory conditions.

Thus the present invention also provides a pharmaceutical composition comprising as active ingredients a novel TXA_2 receptor antagonist of the formula (I) as hereinbefore defined and a TXA_2 synthetase inhibitor, together with a pharmaceutically acceptable diluent or carrier.

Suitable TXA_2 synthetase inhibitors for inclusion as active ingredients in the composition according to the invention include, for example, the known compounds:-

1) 4-[2-(1H-imidazol-1-yl)ethoxy]benzoic acid, (dazoxiben, R.P. Dickinson, et al, J. Med. Chem., 1985, 28, 1427-1432);
2) 3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-1-propanoic acid, (dazmegrel, R.P. Dickinson, et al, J. Med. Chem., 1986, 29, 342-346);
3) 2-methyl-3-(3-pyridylmethyl)-1H-indole-1-propanoic acid, (European patent 0054417);
4) 3-methyl-2-(3-pyridylmethyl)benzo[b]thiophene-5-carboxylic acid, (UK-49,883, P.E. Cross, R.P. Dickinson, Spec Publ. Royal Soc. Chem. No. 50, p. 268-285, 1984);
5) 1,3-dimethyl-2-(1H-imidazol-1-ylmethyl)-1H-indol-5-carboxylic acid, (R.P. Dickinson et al, J. Med. Chem., 1986, 29, 1643-1650);
6) a carboxy, lower alkoxycarbonyl or carbamoyl substituted benzothiophene, benzofuran or indole as claimed in European patent 0073663, or the novel compound:-

7) 2-methyl-3-(3-pyridyl)-1H-indole-1-pentanoic acid; or any other thromboxane synthetase inhibitor which acts in a synergistic manner and is chemically compatible with the novel compounds of formula (I).

Many of the compounds of the invention also inhibit the thromboxane synthetase enzyme in addition to their action as thromboxane receptor antagonists. Such compounds may therefore be effective in the absence of an additional thromboxane synthetase inhibitor.

The biological activity of the compounds of the invention can be demonstrated using the following in vitro and in vivo assay procedures.

1. Thromboxane A_2 receptor antagonism

Spirally cut rat aortic strips, mounted for isometric tension recording in 20ml organ baths, are bathed in Krebs-bicarbonate solution at 37°C. Following an incubation period of 2 hours under 1 gram resting tension, the tissues are pre-treated with U-46619 (a thromboxane A_2 receptor agonist) for 10 minutes, then washed and the tissues allowed to equilibriate for a further 1 hour. Cumulative doses of U-46619 over the range 1nM-100nM are sequentially included in the bathing fluid and increases in the tissue tension noted.

The test compounds are incubated with the tissue for 15 minutes prior to repeating the cumulative dosing of U-46619 and the ability of the compound to antagonize the thromboxane A_2 receptor is determined from the dose-response curves for U-46619 in the presence of varied concentrations of the test compound.

2. Anaesthetised Rabbits

Thromboxane A_2 receptor antagonism is evaluated ex vivo in anaesthetised rabbits as follows:

New Zealand White rabbits (2-2.5kg) are anaesthetised with fentanyl citrate (0.189mg) and fluanisone (6mg) intramuscularly and midazolam (3mg) intravenously and maintained by an intravenous infusion of fentanyl citrate (0.315mg), fluanisone (1mg) and midazolam (1mg) per hour. After cannulation of the trachea, a carotid artery is cannulated for collection of blood samples. The catheter is kept patent by the presence within the catheter of saline containing heparin (50µ/ml). Control carotid arterial blood samples are taken 25 and 5 minutes prior to administration of the test compound via a marginal ear vein. Two groups of rabbits are used. The first group receives 0.01mg/kg of the test compound followed, at ten minute intervals, by 0.03, 0.1, 0.3, 1.0, 3.0 and 10mg/kg doses; the second group comprises the controls. Carotid arterial blood samples are taken 5 minutes after all doses. At each time point, a 900µl blood sample is immediately mixed with 100µl of trisodium citrate (3.15%). After 90 minutes incubation at room temperature, this sample is mixed in equal proportions with an aggregometry buffer (J. Pharmacol. Methods, 1981, 6, 315) and brought to 37°C. Electrodes for the measurement of electrical impedance are placed in the blood and U-46619 (final concentration 3µM) is added to the blood. Antagonism of platelet thromboxane A_2 receptors by the compound is assessed by comparing the change in electrical impedance produced by U-46619 in compound-treated rabbits with the untreated controls.

3. Conscious Dogs

Thromboxane A_2 receptor antagonism may also be evaluated ex vivo in sling-restrained conscious dogs after oral (p.o.) or intravenous (i.v.) administration of a compound of the invention. The sampling and assaying procedures employed are similar to those described for the ex vivo anaesthetised rabbit experiments.

For administration to man, in the therapy or prevention of diseases or adverse medical conditions in which TXA_2 is implicated as a causative agent, oral dosages of the compounds would be expected to be in the range of from 20-800mg daily for an average adult patient (70kg). Thus for a typical adult patient, individual tablets or capsules contain from 10 to 400mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration as a single dose, or in multiple doses, once or several times a day. Dosages for intravenous administration would typically be within the range of from 5 to 400mg per single dose required. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient, and with the condition being treated. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

For human use, the compounds of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical

practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example enough salts or glucose, to make the solution isotonic with blood.

Thus the invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or biolabile ester thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or biolabile ester thereof, or a pharmaceutical composition containing any of these entities, for use in medicine.

The invention further includes the use of a compound of formula (I), or a pharmaceutically acceptable salt or a biolabile ester thereof, for the manufacture of a medicament for the treatment of disease conditions in which thromboxane A_2 is a causative agent.

In a further aspect, the invention provides a method of treating or preventing disease conditions in which thromboxane A_2 is a causative agent in a mammal (including a human being) which comprises administering to said mammal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, or a biolabile ester thereof.

The invention also includes any novel intermediates disclosed herein.

The synthesis of the compounds of the invention and of the intermediates for use in their preparation are illustrated by the following Examples and Preparations. The purity of the compounds was routinely monitored by thin layer chromatography (TLC) using Merck Kieselgel 60 F_{254} plates and the following solvent systems (SS):

1. Dichloromethane;
2. Dichloromethane:methanol, 95:5;
3. Dichloromethane:methanol:0.880 ammonia, 90:10:1;
4. Toluene:diethylamine, 9:1;
5. Dichloromethane:methanol:0.880 ammonia, 100:20:1;
6. Dichloromethane:ethanol:ammonia, 98:2:0.2;
7. Dichloromethane:ethanol:ammonia, 90:10:1;

^{1}H-Nuclear magnetic reasonance (NMR) spectra were recorded using either a Nicolet QE-300 or a Bruker AC-300 spectrometer and were in all cases consistent with the proposed structures. Chemical shifts are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: s, singlet; d, doublet; t, triplet; m, multiplet and br, broad.

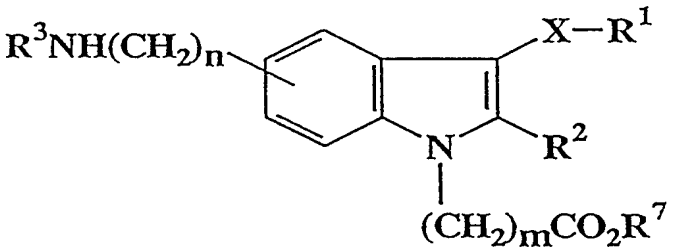
EXAMPLE 1

Methyl 5-[2-[[(4-fluorophenyl)sulphonyl]amino]ethyl]-3-(3-pyridylmethyl)-1H-indole-1-propanoate

4-Fluorobenzenesulphonyl chloride (0.346g) was added portionwise to a stirred solution of methyl 5-(2-aminoethyl)-3-(3-pyridylmethyl)-1H-indole-1-propanoate (0.50g) and triethylamine (0.33g) in dichloromethane (5ml) at room temperature. The mixture was stirred for 30 minutes and then washed with water and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel using dichloromethane/methanol (50:1) as eluant. The product fractions were combined and evaporated to give the title compound as a gum (0.59g). Found: C,62.89; H,5.22; N,8.15. $C_{26}H_{26}FN_3O_4S$ requires: C,63.01; H,5.29; N,8.48%.

EXAMPLES 2 to 22

The compounds of the following formula were prepared as in Example 1 using the appropriate sulphonyl chloride, sulphamoyl chloride or acyl chloride and the appropriate indole compound.



Ex	R^1	R^2	$R^3NH-(CH_2)_n$ position	R^3	R^7	n	m	x	Solvent, Base	m.p. °C	Analytical Data
2	1-imidazolyl	H	5	4-fluoro-phenyl sulphonyl	Me	0	2	CH_2	CH_2Cl_2, Et_3N	Foam	Found: C,57.93; H,4.66; N,12.13; $C_{22}H_{21}FN_4O_4S$ requires: C,57.88; H,4.64; N,12.27%.
3	1-imidazolyl	Me	5	4-fluoro-phenyl sulphonyl	Me	0	2	CH_2	CH_2Cl_2, Pyridine	Foam	Found: C,58.45; H,4.94; N,11.56; $C_{23}H_{23}FN_4O_4S$ requires: C,58.71; H,4.93; N,11.91%.
4	4-fluorophenyl	H	5	4-fluoro-phenyl sulphonyl	Me	0	2	CH_2	CH_2Cl_2, Et_3N	115-118	Found: C,61.55; H,4.24; N,5.90. $C_{29}H_{22}F_2N_2O_4S$ requires: C,61.97; H,4.58; N,5.78%.
5	4-fluorophenyl	H	5	4-chloro-phenyl sulphonyl	Me	0	2	CH_2	CH_2Cl_2, Et_3N	120-123	Found: C,60.14; H,4.35; N,5.56; $C_{25}H_{22}ClFN_2O_4S$ requires: C,59.94; H,4.43; N,5.59%.
6	3-pyridyl	H	5	4-chloro-phenyl sulphonyl	Me	0	2	direct link	CH_2Cl_2, Et_3N	176-178	Found: C,58.96; H,4.13; N,8.79; $C_{23}H_{20}ClN_3O_4S$ requires: C,58.78; H,4.29; N,8.94%.

Ex	R^1	R^2	$R^3NH-(CH_2)_n$ position	R^3	R^7	n	m	x	Solvent, Base	m.p. °C	Analytical Data
7	3-pyridyl	H	5	4-chloro-phenyl sulphonyl	Et	0	3	direct link	CH_2Cl_2, Et_3N	209-211	Found: C,60.11; H,4.83; N,8.33; $C_{25}H_{24}ClN_3O_4S$ requires: C,60.29; H,4.86; N,8.44%.
8	3-pyridyl	H	5	4-fluoro-phenyl sulphonyl	Me	0	2	CH_2	CH_2Cl_2, Et_3N	Foam	Found: C,61.66; H,4.63; N,8.95; $C_{24}H_{22}FN_3O_4S$ requires: C,61.65; H,4.74; N,8.99%.
9	3-pyridyl	H	5	4-fluoro-phenyl sulphonyl	Me	0	3	CH_2	CH_2Cl_2, Et_3N	Foam	Found: C,63.01; H,5.35; N,8.32; $C_{26}H_{26}FN_3O_4S$ requires: C,63.01; H,5.29; N,8.48%.
10	1-imidazolyl	Me	5	4-fluoro-phenyl sulphonyl	Me	2	2	CH_2	CH_2Cl_2, Pyridine	Foam	Rf. 0.55(SS3) δ ($CDCl_3$): 2.47(3H,s), 2.74-2.87(4H,m), 3.24(2H,m), 3.69(3H,s), 4.43(2H,t), 4.62(1H,t), 5.20(2H,s), 6.86(1H,s), 6.92(1H,dd), 7.02 (1H,s), 7.05-7.15 (3H,m), 7.23(1H,d), 7.49(1H,s), 7.77(2H,m).

Ex	R^1	R^2	$R^3NH-(CH_2)_n$ position	R^3	R^7	n	m	x	Solvent, Base	m.p. °C	Analytical Data
11	1-imidazolyl	Me	4	4-fluoro-phenyl sulphonyl	Me	2	2	CH_2	CH_2Cl_2, DMAP	Foam	Found: C,59.98; H,5.53; N,10.94; $C_{25}H_{27}FN_4O_4S$ requires: C,60.22; H,5.46; N,11.24%.
12	3-pyridyl	H	5	methyl-sulphonyl	Me	2	2	CH_2	CH_2Cl_2, Et_3N	Gum	Found: C,59.37; H,5.89; N,9.71; $C_{21}H_{25}N_3O_4S$. $0.1CH_2Cl_2$ requires: C,59.77; H,5.99; N,9.91%.
13	3-pyridyl	H	5	dimethyl-amino-sulphonyl	Me	2	2	CH_2	CH_2Cl_2, DMAP/ Et_3N (1.5:1)	Gum	Rf. 0.6(SS3) δ ($CDCl_3$): 2.75(6H,s), 2.82(2H,t), 2.94(2H,t), 3.34(2H,m), 3.67(3H,s), 4.08(2H,s), 4.14(1H,t), 4.42(2H,t), 6.87(1H,s), 7.08(1H,d), 7.20-7.24(1H,m), 7.29-7.32 (2H,m), 7.55(1H,d), 8.46(1H,d), 8.60(1H,s).
14	3-pyridyl	H	5	3-methyl-butanoyl	Me	2	2	CH_2	CH_2Cl_2, Et_3N	Gum	Found: C,68.52; H,7.09; N,9.59; $C_{25}H_{31}N_3O_3$. $0.25CH_2Cl_2$ requires: C,68.49; H,7.17; N,9.49%.

Ex.	R^1	R^2	$R^3NH-(CH_2)_n$ position	R^3	R^7	n	m	X	Solvent, Base	m.p. °C	Analytical Data
15	3-pyridyl	H	4	4-fluoro-sulphonyl	Me	2	2	CH_2	CH_2Cl_2, Et_3N	Gum	Rf. 0.6(SS3) δ ($CDCl_3$): 2.78(2H,t), 3.00(2H,t), 3.13(2H,m), 3.65(3H,s), 4.13(2H,s), 4.35-4.44(3H,m), 6.72 (1H,s), 6.74(1H,d), 7.07-7.24(5H,m), 7.41(1H,d), 7.74(1H,m), 8.44(2H,m).
16	3-pyridyl	H	4	dimethyl-amino sulphonyl	Me	2	2	CH_2	CH_2Cl_2, Et_3N	Gum	Rf. 0.5(SS3) δ ($CDCl_3$): 2.70(6H,s), 2.79(2H,m), 3.08(2H,t), 3.26(2H,m), 3.66(3H,s), 4.10(1H,t), 4.23(2H,s), 4.38(2H,t), 6.74(1H,s), 6.88(1H,d), 7.13-7.23 (3H,m), 7.46(1H,d), 8.46-8.49(2H,m).
17	3-pyridyl	H	4	3-methyl butanoyl	Me	2	2	CH_2	CH_2Cl_2, Et_3N/ DMAP(1:1)	113-115	Found: C,71.61; H,7.11; N,9.96; $C_{25}H_{31}N_3O_3$ requires: C,71.23; H,7.41; N,9.97%.

Ex	R^1	R^2	$R^3NH-(CH_2)_n$ position	R^3	R^7	n	m	x	Solvent, Base	m.p. °C	Analytical Data
18	3-pyridyl	Me	5	4-fluoro-phenyl sulphonyl	Me	2	2	CH_2	CH_2Cl_2, Et_3N	Gum	Rf. 0.55(SS2) δ ($CDCl_3$): 2.39(3H,s), 2.71-2.80(4H,m), 3.17-3.24(2H,m), 3.67 (3H,s), 4.01(2H,s), 4.34-4.43 (3H,m), 6.85(1H,d), 7.02 (1H,s), 7.05-7.15 (3H,m), 7.20(1H,d), 7.39(1H,d), 7.70-7.75 (2H,m), 8.40(1H,d), 8.49(1H,s).
19	3-pyridyl	Me	5	4-iodo-phenyl-sulphonyl	Me	2	2	CH_2	CH_2Cl_2, Et_3N	Foam	Found: C,52.89; H,4.55; N,6.75; $C_{27}H_{28}IN_3O_4S$ requires: C,52.51; H,4.57; N,6.81%.
20	3-pyridyl	Me	5	4-trifluoro-methyl phenyl sulphonyl	Me	2	2	CH_2	CH_2Cl_2, Et_3N	Foam	Found: C,59.99; H,5.09; N,7.34; $C_{28}H_{28}F_3N_3O_4S$ requires: C,60.09; H,5.04; N,7.51%.

Ex	R^1	R^2	$R^3NH-(CH_2)_n$ position	R^3	R^7	n	m	x	Solvent, Base	m.p. °C	Analytical Data
21	3-pyridyl	Me	4	4-fluoro-phenyl sulphonyl	Me	2	2	CH_2	CH_2Cl_2, Et_3N	Gum	Rf. 0.7(SS3) δ ($CDCl_3$): 2.35(3H,s), 2.76(2H,t), 2.89(2H,t), 3.05(2H,m), 3.68(3H,s), 4.14(2H,s), 4.39-4.48 (3H,m), 6.70(1H,d), 7.05-7.12(4H,m), 7.20-7.26(2H,m), 7.68-7.72(2H,m), 8.33-8.38 (2H,m).
22	H	H	5	4-chloro-phenyl sulphonyl	Me	O	2	direct link	CH_2Cl_2, Et_3N	Gum	Found: C,55.21; H,4.36; N,6.74; $C_{18}H_{17}ClN_2O_4S$ requires: C,55.04; H,4.36; N,7.13%.
23	H	H	5	4-fluoro-phenyl sulphonyl	Me	O	2	direct link	CH_2Cl_2, Et_3N	Gum	Found: C,57.41; H,4.61; N,7.32; $C_{18}H_{17}FN_2O_4S$ requires: C,57.44; H,4.55; N,7.44%.

Ex	R^1	R^2	$R^3NH-(CH_2)_n$ position	R^3	R^7	n	m	x	Solvent, Base	m.p. °C	Analytical Data
24	4-fluoro-phenyl	H	5	Phenyl-sulphonyl	Me	O	2	CH_2	CH_2Cl_2, Et_3N	109-112	Found: C,64.65; H,5.05; N,5.91; $C_{25}H_{23}FN_2O_4S$ requires: C,64.36; H,4.97; N,6.00%.
25	4-fluoro-phenyl	H	5	4-trifluoro-methyl-phenyl-sulphonyl	Me	O	2	CH_2	CH_2Cl_2, Et_3N	100-103	Found: C,58.30; H,4.09; N,5.38; $C_{26}H_{22}F_4N_2O_4S$ requires: C,58.42; H,4.15; N,5.24%.
26	4-fluoro-phenyl	H	5	4-methoxy-phenyl-sulphonyl	Me	O	2	CH_2	CH_2Cl_2, Et_3N	161-162	Found: C,62.91; H,5.00; N,5.43; $C_{26}H_{25}FN_2O_5S$ requires: C,62.89; H,5.07; N,5.64%.
27	4-fluoro-phenyl	H	5	4-methyl-phenyl-sulphonyl	Me	O	2	CH_2	CH_2Cl_2, Et_3N	145-148	Found: C,65.06; H,5.32; N,5.85; $C_{26}H_{25}FN_2O_4S$ requires: C,64.98; H,5.24; N,5.83%.

EXAMPLE 28

Methyl 5-[[(2-cyclopropyl)acetyl]amino]ethyl-3-(3-pyridylmethyl))-1H-indole-1-propanoate

A mixture of cyclopropylacetic acid (0.25g) and carbonyldiimidazole (0.288g) in dry tetrahydrofuran (9ml) was heated under reflux until evolution of CO_2 ceased. A solution of methyl 5-(2-aminoethyl)-3-(3-pyridylmethyl)-1H-indole-1-propanoate (0.50g) in dry dichloromethane (5ml) was added and the solution was stirred at room temperature for 56 hours and then evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was washed twice with water, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel. Elution with dichloromethane gave starting material, and then further elution with dichloromethane/methanol (19:1) gave pure product. The product fractions were evaporated to give the title compound as a gum (0.497g). Rf. 0.7 (SS3).

δ ($CDCl_3$): 0.10(2H,m), 0.48(2H,m), 0.85(1H,m), 2.10(2H,d), 2.82(2H,t), 2.91(2H,t), 3.57(2H,m), 3.67(3H,s), 4.07(2H,s), 4.42(2H,t), 5.90(1H,br), 6.85(1H,s), 7.08(1H,d), 7.22(1H,m), 7.29-7.32(2H,m), 7.57(1H,d), 8.48(1H,d), 8.57(1H,s).

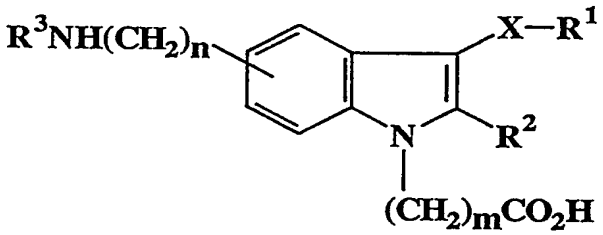
EXAMPLE 29

5-[(4-Fluorophenyl)sulphonyl]amino-3-(3-pyridylmethyl)-1H-indole-1-propanoic acid

A mixture of methyl 5-[(4-fluorophenyl)sulphonyl]-amino-3-(3-pyridylmethyl)-1H-indole-1-propanoate (the product of Example 8) ((1.10g), sodium hydroxide (0.47g), methanol (2ml) and water (10ml) was heated under reflux for 75 minutes and then evaporated to a small volume. The solution was acidified with acetic acid to give a gum which solidified on scratching. The solid was filtered off, washed with water and dried. Crystallisation from ethyl acetate/methanol gave the title compound (0.64g), m.p. 214-215°C. Found: C,61.18; H,4.23; N,9.28. $C_{23}H_{20}FN_3O_4S$ requires: C,60.91; H,4.44; N,9.26%.

EXAMPLES 30-56

The procedure of Example 29 was repeated but using the appropriate starting material to produce compounds of the following formula given in the following Table:



Ex	R^1	R^2	$R^3NH(CH_2)_n$ position	R^3	n	m	x	m.p. °C	Analytical Data
30	1-imidazolyl	H	5	4-fluorophenyl sulphonyl	0	2	CH_2	208-210	Found: C,57.47; H,4.15; N,12.60; $C_{21}H_{19}FN_4O_4S$ requires: C,57.00; H,4.33; N,12.66%.
31	1-imidazolyl	Me	5	4-fluorophenyl sulphonyl	0	2	CH_2	Foam	Rf. 0.1 (SS3) δ ($CDCl_3$): 2.44(3H,s), 2.60 (2H,t), 4.27(2H,t), 5.19(2H,s), 6.77(1H,d), 6.82(1H,s), 6.89 (1H,s), 7.18(1H,s), 7.29-7.33 (3H,m), 7.58(1H,s), 7.66-7.70 (2H,m), 9.97(1H,s).
32	4-fluorophenyl	H	5	4-fluorophenyl sulphonyl	0	2	CH_2	185-188	Found: C,60.78; H,4.19; N,5.74; $C_{24}H_{20}F_2N_2O_4S$ requires: C,61.27; H,4.28; N,5.75%.
33	4-fluorophenyl	H	5	4-chlorophenyl sulphonyl	0	2	CH_2	144-147	Found: C,59.33; H,3.93; N,5.55; $C_{24}H_{20}ClFN_2O_4S$ requires: C,59.20; H,4.14; N,5.75%.
34	3-pyridyl	H	5	4-chlorophenyl sulphonyl	0	2	direct link	235-237	Found: C,58.28; H,3.71; N,9.04; $C_{22}H_{18}ClN_3O_4S$ requires: C,57.95; H,3.98; N,9.22%.
35	3-pyridyl	H	5	4-chlorophenyl sulphonyl	0	3	direct link	199-201	Found: C,58.63; H,4.16; N,8.81; $C_{23}H_{20}ClN_3O_4S$ requires: C,58.78; H,4.29; N,8.94%.
36	3-pyridyl	H	5	4-fluorophenyl sulphonyl	0	3	CH_2	154-156	Found: C,61.80; H,4.68; N,8.91; $C_{24}H_{22}FN_3O_4S$ requires: C,61.65; H,4.74; N,8.99%.
37	1-imidazolyl	Me	5	4-fluorophenyl sulphonyl	2	2	CH_2	165-167	Found: C,58.99; H,5.40; N,10.96; $C_{24}H_{25}FN_4O_4S$ requires: C,59.49; H,5.70; N,11.57%.

Ex	R^1	R^2	$R^3NH(CH_2)_n$ position	R^3	n	m	x	m.p. °C	Analytical Data
38	1-imidazolyl	Me	4	4-fluorophenyl-sulphonyl	2	2	CH_2	Foam	Rf. 0.15 (SS3). δ ($DMSOd_6$): 2.45(3H,s), 2.63 (2H,t), 2.79(2H,t), 2.85(2H,m), 4.37(2H,t), 5.24(2H,s), 6.72 (1H,d), 6.82(1H,s), 6.88(1H,s), 6.98(1H,dd), 7.30-7.40 (3H,m), 7.45(1H,s), 7.79(2H,m), 8.91 (1H,t).
39	3-pyridyl	H	5	4-fluorophenyl-sulphonyl	2	2	CH_2	158-160	Found: C,61.98; H,5.26; N,8.52; $C_{25}H_{24}FN_3O_4S$ requires: C,62.35; H,5.02; N,8.73%.
40	3-pyridyl	H	5	methylsulphonyl	2	2	CH_2	180-182.5	Found: C,60.07; H,5.78; N,10.25; $C_{20}H_{23}N_3O_4S$ requires: C,59.83; H,5.77; N,10.47%.
41	3-pyridyl	H	5	dimethylamino-sulphonyl	2	2	CH_2	160-161	Found: C,58.88; H,5.81; N,12.93; $C_{21}H_{26}N_4O_4S$ requires: C,58.58; H,6.09; N,13.02%.
42	3-pyridyl	H	5	3-methyl-butanoyl	2	2	CH_2	171-172.5	Found: C,71.03; H,6.79; N,10.27; $C_{24}H_{29}N_3O_3$ requires: C,70.73; H,7.17; N,10.31%.

Ex	R^1	R^2	$R^3NH-(CH_2)_n$ position	R^3	n	m	x	m.p. °C	Analytical Data
43	3-pyridyl	H	5	cyclopropyl-acetyl	2	2	CH_2	159-161	Found: C,71.17; H,6.72; N,9.89; $C_{24}H_{27}N_3O_3$ requires: C,71.08; H,6.71; N,10.36%.
44	3-pyridyl	H	4	4-fluorophenyl sulphonyl	2	2	CH_2	93-95	Found: C,62.20; H,5.00; N,8.76; $C_{25}H_{24}FN_3O_4S$ requires: C,62.35; H,5.02; N,8.73%.
45	3-pyridyl	H	4	dimethylamino sulphonyl	2	2	CH_2	179-181	Found: C,58.96; H,6.00; N,12.56; $C_{21}H_{26}N_4O_4S$ requires: C,58.58; H,6.09; N,13.02%.
46	3-pyridyl	H	4	3-methyl-butanoyl	2	2	CH_2	195-196	Found: C,70.97; H,7.11; N,10.26; $C_{24}H_{29}N_3O_3$ requires: C,70.73; H,7.17; N,10.31%.
47	3-pyridyl	Me	5	4-fluorophenyl sulphonyl	2	2	CH_2	197-199	Found: C,62.49; H,5.07; N,8.15; $C_{26}H_{26}FN_3O_4S$ requires: C,63.01; H,5.29; N,8.48%.

Ex	R^1	R^2	$R^3NH-(CH_2)_n$ position	R^3	n	m	x	m.p. °C	Analytical Data
48	3-pyridyl	Me	5	4-iodophenyl sulphonyl	2	2	CH_2	173-176	Found: C,52.02; H,4.27; N,6.81; $C_{26}H_{26}IN_3O_4S$ requires: C,51.74; H,4.34; N,6.96%.
49	3-pyridyl	Me	5	4-trifluoro-methylphenyl-sulphonyl	2	2	CH_2	185-187	Found: C,59.51; H,4.84; N,7.53; $C_{27}H_{26}F_3NO_4S$ requires: C,59.44; H,4.80; N,7.70%.
50	3-pyridyl	Me	4	4-fluorophenyl sulphonyl	2	2	CH_2	218-220	Found: C,63.07; H,5.19; N,8.38; $C_{26}H_{26}FN_3O_4S$ requires: C,63.01; H,5.29; N,8.38%.
51	H	H	5	4-chlorophenyl sulphonyl	0	2	direct link	174-176	Found: C,54.29; H,4.12; N,7.16; $C_{17}H_{15}ClN_2O_4S$ requires: C,53.90; H,3.99; N,7.39%.
52	H	H	5	4-fluorophenyl sulphonyl	0	2	direct link	140-141	Found: C,55.91; H,4.08; N,7.30; $C_{17}H_{15}FN_2O_4S$ requires: C,56.33; H,4.17; N,7.73%.

Ex	R^1	R^2	$R^3NH-(CH_2)_n$ position	R^3	n	m	x	m.p. °C	Analytical Data
53	4-fluoro-phenyl	H	5	phenyl-sulphonyl	O	2	CH_2	178-181	Found: C,63.37; H,4.59; N,5.90; $C_{24}H_{21}FN_2O_4S$ requires: C,63.70; H,4.68; N,6.19%.
54	4-fluoro-phenyl	H	5	4-trifluoro-methylphenyl-sulphonyl	O	2	CH_2	171-175	Found: C,58.14; H,3.61; N,5.01; $C_{25}H_{20}F_4N_2O_4S$ requires: C,57.69; H,3.87; N,5.38%.
55	4-fluoro-phenyl	H	5	4-methoxy-phenyl-sulphonyl	O	2	CH_2	166-168	Found: C,62.14; H,4.73; N,5.93; $C_{25}H_{23}FN_2O_5S$ requires: C,62.23; H,4.80; N,5.81%.
56	4-fluoro-phenyl	H	5	4-methyl-phenyl-sulphonyl	O	2	CH_2	203-206	Found: C,64.12; H,4.79; N,5.95; $C_{25}H_{23}FN_2O_4S$ requires: C,64.36; H,4.97; N,6.00%.

EXAMPLE 57

1,2-Dimethyl-5-[(4-fluorophenyl)sulphonyl]amino-1H-indole-1-propanoic acid

A solution of 5-[(4-fluorophenyl)sulphonyl]amino-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-1-propanoic acid (0.30g) in ethanol (5ml) and acetic acid (5ml) was hydrogenated for 24 hours at 50°C and 4.5 atm. in the presence of 10% palladium on carbon (30mg). The mixture was filtered and the residue was washed with ethanol. The filtrate and washings were combined and evaporated, and the residue was partitioned between ethyl acetate and water. The organic layer was washed twice with water and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel, using dichloromethane/methanol (19:1) as eluant. The product fractions were combined and evaporated to give the title compound as a gum (0.035g), Rf. 0.75(SS7).

δ ($DMSOd_6$): 1.96(3H,s), 2.25(3H,s), ca 2.48(2H,t), 4.20(2H,t), 6.70(1H,d), 6.98(1H,s), 7.15(1H,d), 7.26(2H,m), 7.66(2H,m), 9.71(1H,s).

EXAMPLE 58

Pharmaceutical Capsules

	mg/capsule
Thromboxane A_2 Antagonist	50.0
Thromboxane Synthetase Inhibitor	150.0
Starch	49.0
Magnesium stereate BP	1.0
	250 mg

The thromboxane A_2 antagonist and the thromboxane synethase inhibitor are sieved and blended with the starch and the excipients. The mix is filled into size No. 2 hard gelatin capsules, using suitable machinery. Capsules of other strengths or with different ratios of active ingredients may be prepared in a similar manner.

Regarding toxicity, the compounds of Examples 33,41,42,46 and 49 have each been administered acutely to dogs at doses up to 10mg/kg orally. No signs of toxicity were observed.

PREPARATION 1

3-(1H-Imidazol-1-ylmethyl)-5-nitro-1H-indole

A mixture of N,N-dimethyl-5-nitro-1H-indole-3-methanamine (J.Med.Chem.,9,140,(1966)) (9.10g) and imidazole (2.96g) in xylene (120ml) was heated under reflux for 2.5 hours and then cooled. The solid was filtered off, washed with ether and dried to give the title compound (9.40g), m.p. 230-232°C (from ethyl acetate/methanol). Found: C,59.85; H,4.39; N,22.80. $C_{12}H_{10}N_4O_2$ requires: C,59.50; H,4.16; N,23.13%.

PREPARATION 2

3-(1H-Imidazol-1-ylmethyl)-2-methyl-5-nitro-1H-indole

Treatment of 2,N,N-trimethyl-5-nitro-1H-indole-3-methanamine (J.Org.Chem.,28,2921(1963)) (5.60g) with imidazole (1.90g) in xylene (100ml) according to the method of Preparation 1 gave the title compound (5.50g), m.p. 240-242°C. Found: C,61.02; H,4.41; N,21.68. $C_{13}H_{12}N_4O_2$ requires: C,60.92; H,4.72; N,21.87%.

PREPARATION 3

5-Nitro-3-(3-pyridylmethyl)-1H-indole

a) 3-(3-Pyridyl)propanal

Dimethylsulphoxide (18.9ml) in dry dichloromethane (120ml) was added over 20 minutes to a stirred solution of oxalyl chloride (11.55ml) in dry dichloromethane (225ml) at -70°C. The mixture was stirred at -70°C for 10 minutes and then a solution of 3-(3-pyridyl)propanol (16.56g) in dry dichloromethane (120ml) was added with stirring over 20 minutes. Stirring was continued at -70°C for a further 20 minutes and then triethylamine (50.55ml) was added dropwise and the temperature was allowed to rise to room

temperature. Water (200ml) was added and the layers were separated. The organic layer was washed twice with water, dried ($MgSO_4$) and evaporated. The residue was distilled to give the title compound as an oil (8.80g), b.p. 88-92°C @ 0.3mm., Rf. 0.15 (SS2). δ ($CDCl_3$): 2.80(3H,t), 2.93(3H,t), 7.18-7.21(1H,m), 7.50(1H,d), 8.40-8.45(2H,m), 9.80(1H,s).

b) 3-(3-Pyridyl)propanal-4-nitrophenylhydrazone

3-(3-Pyridyl)propanal (8.50g) was added to a stirred suspension of 4-nitrophenylhydrazine (9.62g) in ether 150ml. After a minute an orange-brown oil formed which solidified on further stirring. The solid was filtered off to give the title compound pure enough for further reaction (14.05g), m.p. 146-147°C (from ethyl acetate/methanol). Found: C,62.12; H,5.02; N,20.36. $C_{14}H_{14}N_4O_2$ requires: C,62.21; H,5.22; N,20.73%.

c) 5-Nitro-3-(3-pyridylmethyl)-1H-indole

The above hydrazone (15g) was added portionwise to a stirred mixture of polyphosphoric acid (60g) and toluene (180ml). The mixture was then heated at 110°C with stirring for 1 hour and then cooled, poured into water and basified with concentrated aqueous ammonia solution. The aqueous layer was separated and extracted three times with ethyl acetate. The organic layers were combined, washed with water and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel. Elution with dichloromethane/methanol (40:1), gradually increasing the polarity to 25:1, gave the title compound (9.4g), m.p. 154-156°C (from ethyl acetate). Found: C,66.68; H,4.19; N,16.61. $C_{14}H_{11}N_3O_2$ requires: C,66.39; H,4.38; N,16.59%.

PREPARATION 4

5-Nitro-3-(3-pyridyl)-1H-indole

a) 3-(2-EZ-methoxyethenyl)pyridine

Phenyllithium (111ml of 1.8M solution in ether) was added dropwise to a stirred suspension of (methoxymethyl) triphenylphosphonium chloride (68.6g) in dry ether (600ml) at -50°C. The mixture was stirred at -50°C for 2 hours and then allowed to reach 0°C over 30 minutes. 3-Pyridinecarboxaldehyde (10.70g) was added dropwise with stirring, and the mixture was stirred at room temperature for 18 hours. An excess of ammonium chloride solution was then added and the layers were separated. The aqueous layer was separated and washed with ether, and the organic layers were combined and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel initially using ethyl acetate/hexane (1:4) as eluant. The polarity was gradually increased to ethyl acetate/hexane (1:1) to give the pure product as an oil (8.82g) which was used directly in the next stage.

b) 3-Pyridineacetaldehyde-4-nitrophenylhydrazone

A solution of 3-(2-EZ-methoxyethenyl)pyridine (3.43g) in ethanol (15ml) and 2N hydrochloric acid (25ml) was heated under reflux for 1 hour and then cooled. 4-nitrophenylhydrazine (3.89g) was added portionwise with stirring to give a solution which deposited a yellow solid. The mixture was cooled in ice and the solid was filtered off, washed with isopropanol, ether and then dried to give the title compound (5.32g), m.p. 212-214°C. Found: C,53.54; H,4.51; N,19.00. $C_{13}H_{12}N_4O_2$ requires: C,53.34; H,4.48; N,19.14%.

c) 5-Nitro-3-pyridyl-1H-indole

The above hydrazone (4.30g) was added to ice-cooled concentrated sulphuric acid (43ml) at such a rate that the temperature did not rise above 20°C. The mixture was stirred at room temperature for 1 hour and was then stirred at 30°C for a further 1 hour. It was carefully poured into 500ml of ice water and the solution was basified with concentrated aqueous ammonia solution with cooling. The mixture was extracted twice with ethyl acetate and the combined extracts were washed with water and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel. Elution with ethyl acetate followed by ethyl acetate/methanol (19:1) gave the title compound (1.25g), m.p. >265°C. Found: C,65.34; H,3.41; N,17.69. $C_{13}H_{19}N_3O_2$ requires: C,65.26; H,3.79; N,17.57%.

PREPARATION 5

3-(4-Fluorophenylmethyl)-5-nitro-1H-indole

a) 3-(4-Fluorophenyl)propanal

Di-isobutylaluminium hydride (75ml of 1.0M solution in toluene) was added dropwise to a stirred solution of ethyl (4-fluorophenyl)-propanoate (J.Org.Chem.,31, 1524 (1966)) (11.84g) in toluene (130ml) at -70°C. The solution was stirred at -70°C for 90 minutes, then ca 100ml of 15% ammonium chloride solution was added dropwise and the temperature was allowed to reach room temperature. The organic layer was separated, dried (Na_2SO_4) and evaporated to give an oil which was chromatographed on silica gel. Elution with dichloromethane/hexane (3:1) gave the title compound as an oil (7.05g), Rf. 0.7(SS1).

δ ($CDCl_3$): 2.77(2H,t), 2.93(2H,t), 6.94-7.00(2H,m), 7.13-7.17(2H,m), 9.81(1H,s).

b) 3-(4-Fluorophenyl)propanal-4-nitrophenylhydrazone

A solution of 3-(4-fluorophenyl)propanal (7.0g) in ether (50ml) was added to a stirred suspension of 4-nitrophenylhydrazine (7.0g) in ether (150ml), followed by sufficient ethyl acetate to achieve a clear solution. The solution was filtered and evaporated and the residue was crystallised from ethyl acetate/hexane to give the title compound (5.48g), m.p. 125-127°C. Found: C,62.81; H,4.87; N,14.44. $C_{15}H_{14}FN_3O_2$ requires: C,62.71; H,4.91; N,14.63%.

Evaporation of the filtrate and trituration of the residue with hexane gave a further 5.39g of title compound pure enough for further reaction.

c) 3-(4-Fluorophenylmethyl)-5-nitro-1H-indole

The above hydrazone (10.5g) was added portionwise to a stirred mixture of polyphosphoric acid (45g) and toluene (120ml) at 40°C. The resulting mixture was stirred at 105-110°C for 75 minutes and then cooled. The toluene layer was decanted off and the residue was poured into water. The mixture was extracted twice with toluene and all the organic layers were combined, washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a solid which was crystallised from ethyl acetate to give the title compound (2.20g), m.p. 142-144°C. Found: C,66.44; H,3.68; N,10.00. $C_{15}H_{11}FN_2O_2$ requires: C,66.66; H,4.10; N,10.37%.

PREPARATION 6

5-Bromo-3-(3-pyridylmethyl)-1H-indole

Methyl magnesium iodide (4.0ml of 3M solution in ether) was added over 5 minutes to a stirred solution of 5-bromo-1H-indole (1.96g) in dry tetrahydrofuran (25ml) at 0°C, the resulting suspension was stirred at room temperature for 45 minutes. Separately, a solution of 3-(chloromethyl)pyridine was prepared by partitioning 3-(chloromethyl)pyridine hydrochloride (1.97g) between water and dichloromethane followed by dropwise addition of triethylamine with shaking until the pH of the aqueous layer was >7. The layers were separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined, dried ($MgSO_4$) and evaporated to ca 25ml. The solution was dried for a further 20 minutes by the addition of 3A molecular sieves. It was then added dropwise with stirring to the suspension of the indole Grignard reagent. The mixture was heated at 75°C for 2 hours with stirring and then allowed to cool to room temperature. A solution of ammonium chloride (1.0g) in water (30ml) was added with stirring and the resulting mixture was extracted several times with ethyl acetate. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel using dichloromethane/methanol (50:1) as eluent. Impurity was eluted first followed by pure product. The product fractions were combined and evaporated and the residue was crystallised from ether to give the title compound (0.798g), m.p. 126-128°C. Found: C,58.76; H,3.92; N,9.67. $C_{14}H_{11}BrN_2$ requires: C,58.55; H,3.86; N,9.76%.

PREPARATION 7

4-Bromo-3-(3-pyridylmethyl)-1H-indole

Treatment of 4-bromo-1H-indole (J.Org.Chem.,48 2066(1983)) (16.95g) with methyl magnesium bromide (34.6ml of 3M solution in ether) followed by a dichloromethane solution of 3-(chloromethyl)pyridine (prepared from 17.02g of 3-(chloromethyl)pyridine hydrochloride) according to the method of Preparation 6 gave the title compound (7.80g), m.p. 173-174°C. Found: C,58.90; H,3.88; N,9.80. $C_{14}H_{11}BrN_2$ requires: C,58.55; H,3.86; N,9.76%.

PREPARATION 8

5-Bromo-2-methyl-3-(3-pyridylmethyl)-1H-indole

A solution of 5-bromo-2-methyl-1H-indole (J.Chem.Soc., 1428 (1965)) (2.0g) and 3-pyridinecarboxaldehyde (1.02g) in dry dichloromethane (20ml) was added dropwise over 10 minutes to a stirred solution of triethylsilane (3.30g) in trifluoroacetic acid (20ml) at 0°C. The solution was stirred at 0°C for 30 minutes and then evaporated under vacuum, keeping the temperature below 35°C. The residue was dissolved in dichloromethane, and the solution was washed with 2N sodium hydroxide, water and dried ($MgSO_4$). The solution was evaporated and the residue was chromatographed on silica gel, using dichloromethane/methanol (50:1) as eluent. The product fractions were combined and evaporated, and the residue was crystallised from ether to give the title compound (2.15g), m.p. 188-190°C. Found: C,59.62; H,4.43; N,9.26. $C_{15}H_{13}BrN_2$ requires: C,59.82; H,4.35; N,9.30%.

PREPARATION 9

4-Bromo-2-methyl-1H-indole and 6-bromo-2-methyl-1H-indole

3-Bromophenylhydrazine hydrochloride (26.5g) was partitioned between ether and excess 2N sodium hydroxide solution. The ether layer was separated, washed with brine, dried ($MgSO_4$) and evaporated. The residue was redissolved in ether (25ml) and the solution was cooled in ice. Acetone (25ml) was added and the mixture was allowed to stand for 20 minutes and then evaporated. The residue was dissolved in acetone (25ml), the solution was evaporated and the residue azeotroped with xylene. The residue was dissolved in xylene (30ml) and the solution was added dropwise to stirred polyphosphoric acid (200g) at 90°C. The mixture was stirred at 100°C for 4 hours and then cooled and poured into ice water with stirring. The mixture was extracted twice with ether, and the combined extracts were washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel using dichloromethane/hexane (1:4) as eluent. The product fractions were combined and evaporated, and the residue was crystallised twice from hexane to give 6-bromo-2-methyl-1H-indole (8.70g), m.p. 132-134°C.

δ ($CDCl_3$): 2.38(3H,s), 6.15(1H,s), 7.12(1H,dd), 7.32(1H,d), 7.36(1H,d), 7.77(1H,br).

The hexane filtrates were combined and evaporated, and the residue was chromatographed as before to give an oil (8.35g) shown by nmr to consist of a mixture of 4-bromo-2-methyl-1H-indole and 6-bromo-2-methyl-1H-indole in the ratio 3:1.

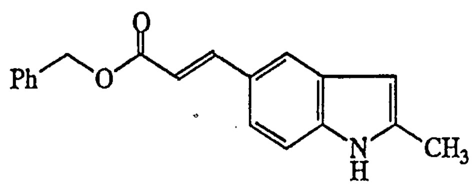
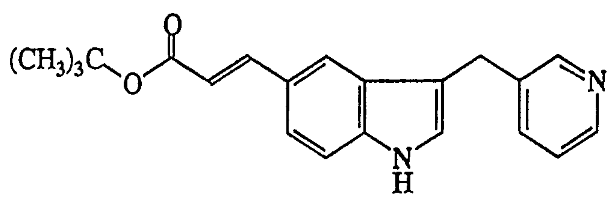
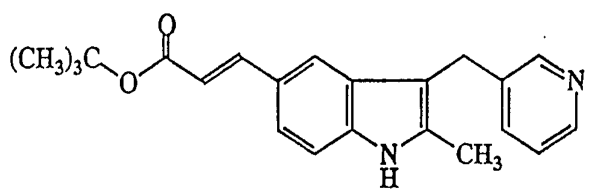
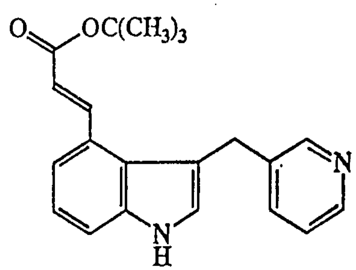
δ ($CDCl_3$) for the 4-bromo isomer: 2.45(3H,s), 6.29(1H,s), 6.95(1H,dd), 7.21-7.27(2H,m), 7.96(1H,br).

PREPARATION 10

Benzyl (E)-3-(2-methyl-1H-indol-4-yl)-2-propenoate

A mixture of 4-bromo-2-methyl-1H-indole (containing 25% of the 6-bromo isomer) (8.30g), palladium (II) acetate (0.45g), tri-o-tolylphosphine (1.22g), benzyl acrylate (9.76g) and triethylamine (8.36ml) in acetonitrile (8ml) was heated in an oil bath at 140°C under an atmosphere of nitrogen for 2 hours. The mixture was cooled and partitioned between dichloromethane and water. The organic layer was separated, washed three times with water and dried ($MgSO_4$). Evaporation of the solvent gave an oil which was chromatographed on silica gel. Elution with dichloromethane/hexane (1:1) first gave impurity followed by pure product. The product fractions were evaporated and the residue was triturated with ether to give the title compound (6.60g), m.p. 135-136°C. Found: C,77.98; H,6.10; N,4.71. $C_{19}H_{17}NO_2$ requires: C,78.33; H,5.88; N,4.81%.
Further elution with dichloromethane/hexane (4:1) gave benzyl (E)-3-(2-methyl-1H-indol-6-yl)-2-propenoate (2.0g), m.p. 164-165°C. Found: C,78.53; H,6.06; N,4.74. $C_{19}H_{17}NO_2$ requires: C,78.33; H,5.88; N,4.81%.

The following compounds were prepared similarly.

Structure	m.p. °C	Analytical Data
	139-141	Found: C,77.74; H,5.92; N,4.52; $C_{18}H_{17}NO_2$ requires: C,78.33; H,5.88; N,4.81%.
	160-161	Found: C,75.47; H,6.46; N,8.33; $C_{21}H_{22}N_2O_2$ requires: C,75.42; H,6.63; N,8.38%.
	121-124	Found: C,75.53; H,6.87; N,8.12; $C_{22}H_{24}N_2O_2$ requires C,75.83; H,6.94; N,8.04%.
	146-148	Found: C,75.12; H,6.40; N,8.29; $C_{21}H_{22}N_2O_2$ requires: C,75.42; H,6.63; N,8.38%.

PREPARATION 11

Benzyl (E)-3-[2-methyl-3-(3-pyridylmethyl)-1H-indol-4-yl]-2-propenoate

A solution of benzyl (E)-3-[2-methyl-1H-indol-4-yl]-2-propenoate (4.75g) and pyridine-3-carboxaldehyde (2.10g) in dry dichloromethane (45ml) was added dropwise to a stirred solution of triethylsilane (7.82ml) in trifluoroacetic acid (40ml) at 0°C. The solution was stirred, allowing the temperature to rise to room temperature, for 45 minutes and then evaporated. The residue was partitioned between dichloromethane and dilute aqueous ammonia solution. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with water and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel. Elution with dichloromethane gave impurity, and further elution with dichloromethane/methanol (19:1) gave pure product. The product fractions were evaporated and the residue was triturated with ether to give the title compound (2.19g), m.p. 180-182°C, Rf. 0.35(SS1). δ ($CDCl_3$): 2.43(3H,s), 4.21(2H,s), 5.21(2H,s), 6.30(1H,d), 7.01-7.11(2H,m), 7.28-7.42(8H,m), 8.19(1H,d), 8.22(1H,s), 8.38(2H,s).

PREPARATION 12

Benzyl (E)-3-[3-(dimethylaminomethyl)-2-methyl-1H-indol-5-yl]-2-propenoate

Dimethylamine (3.35ml of 33% solution in methylated spirit) was added to a stirred mixture of benzyl (E)-3-(2-methyl-1H-indol-5-yl)-2-propenoate (6.50g) in a mixture of acetic acid (14ml) and tetrahydrofuran (15ml) at 0°C, followed by the dropwise addition of formaldehyde (1.75ml of

40% aqueous solution). The mixture was stirred at room temperature for 3 hours and then diluted with ethyl acetate. 2N sodium hydroxide was added dropwise with stirring until the pH of the aqueous layer was ca.9. The mixture was filtered, and the residue was washed with water followed by ethyl acetate and then dried to give the title compound (6.58g), m.p. 174-177°C. Found: C,75.85; H,6.83; N,7.53. $C_{22}H_{24}N_2O_2$ requires: C,75.83; H,6.94; N,8.04%.

PREPARATION 13

Benzyl (E)-3-[3-(dimethylaminomethyl)-2-methyl-1H-indol-4-yl]-2-propenoate

Treatment of benzyl (E)-3-(2-methyl-1H-indol-4-yl)-2-propenoate (6.20g) with dimethylamine (3.2ml of 33% solution in methylated spirit), and formaldehyde (1.68ml of 40% aqueous solution) in acetic acid (13ml) and tetrahydrofuran (15ml) according to the method of Preparation 12 gave the title compound as a foam (7.45g), Rf. 0.3(SS3).
δ ($CDCl_3$): 2.25(6H,s), 2.37(3H,s), 3.49(2H,s), 5.28(2H,s), 6.48(1H,d), 7.07(1H,dd), 7.22-7.44(7H,m), 8.08(1H,s), 9.07(1H,d).

PREPARATION 14

Benzyl (E)-3-[3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indol-5-yl]-2-propenoate

A mixture of benzyl (E)-3-[(3-dimethylaminomethyl)-2-methyl-1H-indol-5-yl]-2-propenoate (7.65g) and imidazole (1.64g) in dry dioxan (50ml) was heated under reflux for 4 hours. The solution was cooled, filtered and evaporated. The residue was chromatographed on silica gel using dichloromethane/methanol (19:1) as eluent. Evaporation of the product fractions and trituration of the residue with ether gave the title compound (4.85g), m.p. 120-122°C. Found: C,74.43; H,5.70; N,11.25. $C_{23}H_{21}N_3O_2$ requires: C,74.37; H,5.70; N,11.32%.

PREPARATION 15

Benzyl (E)-3-[3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indol-4-yl]-2-propenoate

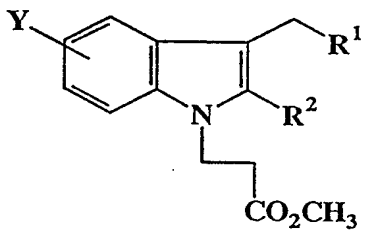
A mixture of benzyl (E)-3-[(3-dimethylaminomethyl)-2-methyl-1H-indol-4-yl]-2-propenoate (7.45g), and imidazole (1.57g) in xylene (50ml) was heated under reflux for 6 hours and the solution was evaporated. The residue was chromatographed on silica gel using dichloromethane/methanol as eluent. Evaporation of the product fractions and trituration of the residue with ether gave the title compound (3.85g), m.p. 207-208.5°C. Found: C,74.48; H,5.64; N,11.31. $C_{23}H_{21}N_3O_2$ requires: C,74.37; H,5.70; N,11.32%.

PREPARATION 16

Methyl 5-nitro-3-(3-pyridylmethyl)-1H-indole-1-propanoate

Benzyltrimethylammonium hydroxide (0.8ml of 40% solution in methanol) was added to a stirred mixture of 5-nitro-3-(3-pyridylmethyl)-1H-indole (7.34g) and methyl acrylate (3.0g) in dioxan (140ml) and the resulting solution was stirred for 75 minutes and then evaporated. The residue was partitioned between water and ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate. The organic layers were combined, washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a solid which was crystallised from ethyl acetate/hexane to give the title compound (7.33g), m.p. 101-102°C. Found: C,63.85; H,4.86; N,12.37. $C_{18}H_{17}N_3O_4$ requires: C,63.71; H,5.05; N,12.38%.

The following compounds were prepared similarly.



R^1	R^2	Y	m.p. °C	Analytical Data
1-imidazolyl	H	5-Nitro	152-154	Found: C,58.88; H,5.01; N,17.07; $C_{16}H_{16}N_4O_4$ requires: C,58.53; H,4.91; N,17.07%.
1-imidazolyl	CH_3	5-Nitro	150-151	Found: C,59.82; H,5.28; N,16.41; $C_{17}H_{18}N_4O_4$ requires: C,59.64; H,5.30; N,16.37%.
1-imidazolyl	CH_3	5-(E)-$PhCH_2O_2CCH$=CH-	113-116	Found: C,70.97; H,5.95; N,9.12; $C_{12}H_{27}N_3O_4$ requires: C,70.88; H,5.95; N,9.19%.
1-imidazolyl	CH_3	4-(E)-$PhCH_2O_2CCH$=CH-	-	Found: C,70.88; H,5.90; N,8.91; $C_{27}H_{27}N_3O_4$ requires: C,70.88; H,5.95; N,9.19%.

R^1	R^2	Y	m.p. °C	Analytical Data
3-pyridyl	H	5-(E)-t-BuO_2CCH=CH-	-	Found: C,71.04; H,6.67; N,6.43; $C_{25}H_{28}N_2O_4$ requires: C,71.40; H,6.71; N,6.66%.
3-pyridyl	H	4-(E)-t-BuO_2CCH=CH-	86-88	Found: C,71.69; H,6.59; N,6.77; $C_{25}H_{28}N_2O_4$ requires: C,71.40; H,6.71; N,6.66%.
3-pyridyl	CH_3	5-(E)-t-BuO_2CCH=CH-	91-93	Found: C,72.17; H,6.96; N,6.42; $C_{26}H_{30}N_2O_4$ requires: C,71.86; H,6.96; N,6.45%.
3-pyridyl	CH_3	4-(E)-t-BuO_2CCH=CH-	-	Found: C,74.34; H,6.07; N,6.05; $C_{29}H_{28}N_2O_4$ requires: C,74.37; H,6.03; N,5.98%.

PREPARATION 17

Ethyl 5-nitro-3-(3-pyridyl)-1H-indole-1-butanoate

5-Nitro-3-(3-pyridyl)-1H-indole (0.60g) was added portionwise to a stirred suspension of sodium hydride (0.11g of 60% dispersion in mineral oil) in dry N,N-dimethylformamide (10ml) at room temperature, and the mixture was stirred for 30 minutes. Ethyl 4-bromobutanoate (0.40g) was added and the mixture was stirred for 18 hours. Further sodium hydride (0.11g of 60% dispersion) was added, the mixture was stirred for 30 minutes and then further ethyl 4-bromobutanoate (0.40g) was added. Stirring was continued for an additional 4 hours and then the mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed twice with water and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed using dichloromethane/methanol (100:1) as eluent. The product fractions were combined and evaporated, and the residue was triturated with ether to give the title compound (0.51g), m.p. 76-78°C. Found: C,64.92; H,5.48; N,11.95. $C_{19}H_{19}N_3O_4$ requires: C,64.58; H,5.42; N,11.89%.

PREPARATION 18

Methyl 5-nitro-3-(3-pyridyl)-1H-indole-1-propanoate

Benzyltrimethylammonium hydroxide (0.17ml of 40% solution in methanol) was added to a stirred suspension of 5-nitro-3-(3-pyridyl)-1H-indole (0.95g) and methyl acrylate (0.41g) in a mixture of tetrahydrofuran (10ml) and dioxan (15ml), and the mixture was stirred at room temperature for 2 hours. Methanol (10ml) was added to give a clear solution followed by further methyl acrylate (0.41g) and benzyltrimethylammonium hydroxide solution (0.17ml) and stirring was continued for an additional 18 hours. Potassium t-butoxide (100mg) was added and stirring was continued

for a further 6 hours and the solution was evaporated. The residue was partitioned between ethyl acetate and water and the organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent gave a solid which was crystallised from dichloromethane/hexane to give the title compound (0.48g), m.p. 123-125°C. Found: C,62.85; H,4.62; N,12.91. $C_{17}H_{15}N_3O_4$ requires: C,62.76; H,4.65; N,12.92%.

PREPARATION 19

Methyl 3-(4-fluorophenylmethyl)-5-nitro-1H-indole-1-propanoate

Tetrabutylammonium bromide (0.262g) and potassium t-butoxide (100mg) were added to a stirred solution of 3-(4-fluorophenylmethyl)-5-nitro-1H-indole (2.20g) and methyl acrylate (0.84g) in dioxan (30ml) and the solution was stirred at room temperature for 66 hours. Further quantities of methyl acrylate (0.5g), tetrabutylammonium bromide (262mg) and potassium t-butoxide (100mg) were added and stirring was continued for an additional 5 hours. The solution was poured into water and the mixture was extracted twice with ether. The combined ether extracts were washed with water, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel using hexane/dichloromethane (1:4) as eluent. The product fractions were combined and evaporated to give the title compound as a gum (1.90g). Found: C,64.43; H,4.39; N,7.65. $C_{19}H_{17}FN_2O_4$ requires: C,64.03; H,4.81; N,7.86%.

PREPARATION 20

Methyl 5-nitro-1H-indole-1-propanoate

Reaction of 5-nitro indole (3.0g) with methyl acrylate (2.29g) in the presence of potassium t-butoxide (0.258g) and tetrabutylammonium bromide according to the method of Preparation 19 gave the title compound (3.0g), m.p. 97-99°C. Found: C,57.86; H,4.84; N,10.78. $C_{12}H_{12}N_2O_4$ requires: C,58.06; H,4.87; N,11.28%.

PREPARATION 21

Methyl 5-(2-carboxyethyl)-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-1-propanoate

A solution of benzyl (E)-3-[3-(1H-imidazol-1-ylmethyl)-1-(2-methoxycarbonylethyl)-2-methyl-1H-indol-5-yl]-2-propenoate (2.0g) in tetrahydrofuran (40ml) was hydrogenated at room temperature and 4.5 atm. in the presence of 10% palladium on carbon (0.20g) until reaction was complete (5 hours). The mixture was filtered and the residue was washed with ethyl acetate. The combined filtrate and washings were evaporated and the residue was triturated with ether to give the title compound (1.52g), m.p. 134-137°C. Found: C,65.31; H,6.35; N,10.70. $C_{20}H_{23}N_3O_4$ requires: C,65.02; H,6.28; N,11.38%.

PREPARATION 22

Methyl 4-(2-carboxyethyl)-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-1-propanoate

Hydrogenation of benzyl (E)-3-[3-(1H-imidazol-1-ylmethyl)-1-(2-methoxycarbonylethyl)-2-methyl-1H-indol-4-yl]-2-propenoate (1.40g) in the presence of 10% palladium on carbon (0.15g) according to the method of Preparation 21 gave the title compound (0.82g), m.p. 136-138°C.

δ ($DMSOd_6$): 2.34(2H,t), 2.57(3H,s), 2.74(2H,t), 2.96(2H,t), 3.54(3H,s), 4.40(2H,t), 5.32(2H,s), 6.78(1H,d), 6.82(1H,s), 6.90(1H,s), 6.98(1H,dd), 7.29(1H,d), 7.43(1H,s).

PREPARATION 23

t-Butyl 1-(2-methoxycarbonylethyl)-3-(3-pyridylmethyl)-1H-indole-5-propanoate

A mixture of t-butyl (E)-3-[1-(2-methoxycarbonylethyl)-3-(3-pyridylmethyl)-1H-indol-5-yl]-2-propenoate (7.86g), 10% palladium on carbon (0.70g) and ammonium formate (5.60g) in a mixture of methanol (40ml) and tetrahydrofuran (40ml) was heated at 60°C for 3 hours and then cooled. The mixture was filtered and the residue was washed with methanol. The filtrate and washings were combined and evaporated, and the residue was partitioned between water and ether. The organic layer was separated and the aqueous layer was extracted with ether. The organic layers were combined, washed with water and dried ($MgSO_4$). Evaporation of the solvent gave the title compound as an oil (7.80g). Found: C,70.51; H,6.98; N,6.54. $C_{25}H_{30}N_2O_4$ requires: C,71.06; H,7.16; N,6.63%.

PREPARATION 24

t-Butyl 1-(2-methoxycarbonylethyl)-3-(3-pyridylmethyl)-1H-indole-4-propanoate

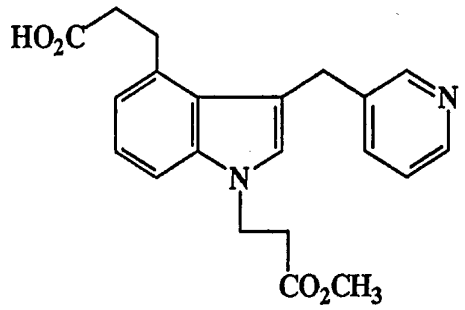
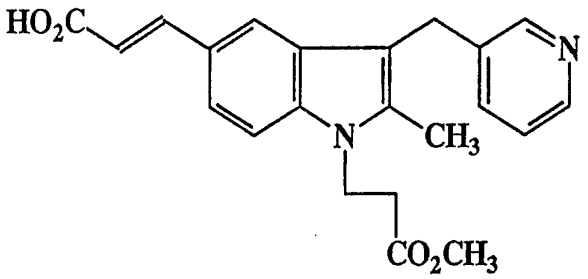
Treatment of t-butyl (E)-3-[1-(2-methoxycarbonylethyl)-3-(3-pyridylmethyl)-1H-indole-4-yl]-2-propenoate (5.15g) with 10% palladium on carbon (0.50g) and ammonium formate (7.71g) according to the method of Preparation 23 gave the title compound, (4.67g) m.p. 80-82°C. Found: C,71.43; H,7.06; N,6.35. $C_{25}H_{30}N_2O_4$ requires: C,71.06; H,7.16; N,6.63%.

PREPARATION 25

Methyl 5-(2-carboxyethyl)-3-(3-pyridylmethyl)-1H-indole-1-propanoate

Trifluoroacetic acid (15ml) was added to a stirred solution of t-butyl 1-(2-methoxycarbonylethyl)-3-(3-pyridylmethyl)-1H-indole-5-propanoate (7.60g) in dry dichloromethane (100ml) at room temperature, and stirring was continued for 18 hours. The solution was evaporated and the residue was azeotroped with toluene and then dissolved in ethyl acetate. Saturated sodium bicarbonate solution was added slowly with shaking until the pH of the aqueous layer was 4-5. The organic layer was then separated, washed with water and dried ($MgSO_4$). The solvent was evaporated and the residue was triturated with ether to give the title compound (5.70g), m.p. 108-110°C. Found: C,68.80; H,6.16; N,7.57%. $C_{21}H_{22}N_2O_4$ requires: C,68.83; H,6.05; N,7.65%.

The following compounds were prepared similarly from the corresponding t-butyl ester.

Structure	m.p. °C	Analytical Data
	199-201	Found: C,68.65; H,6.27; N,7.53. $C_{21}H_{22}N_2O_4$ requires: C,68.83; H,6.05; N,7.65%.
	180-182	Found: C,69.65; H,5.73; N,7.19. $C_{22}H_{22}N_2O_4$ requires: C,67.82; H,5.86; N,7.40%.

PREPARATION 26

Methyl 5-(2-carboxyethyl)-2-methyl-3-(3-pyridylmethyl)-1H-indole-1-propanoate

A mixture of (E)-3-[1-(2-methoxycarbonylethyl)-2-methyl-3-(3-pyridylmethyl)-1H-indol-5-yl]-2-propenoic acid (2.02g), 10% palladium on carbon (0.20g) and ammonium formate (1.68g) in methanol (20ml) and tetrahydrofuran (20ml) was heated at 60°C for 4 hours and then cooled and filtered. The residue was washed with methanol, and the filtrate and washings were combined and evaporated. The residue was triturated with dilute acetic acid to give a gummy solid. The solid was filtered off and boiled with ether to give the title compound as a crystalline solid (1.79g), m.p. 144-146°C. Found: C,69.60; H,6.20; N,7.16. $C_{22}H_{24}N_2O_4$ requires: C,69.45; H,6.36; N,7.37%.

PREPARATION 27

Methyl 4-(2-carboxyethyl)-2-methyl-3-(3-pyridylmethyl)-1H-indole-1-propanoate

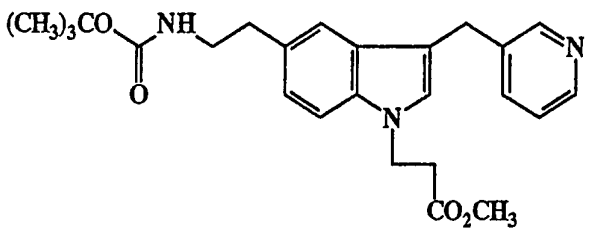
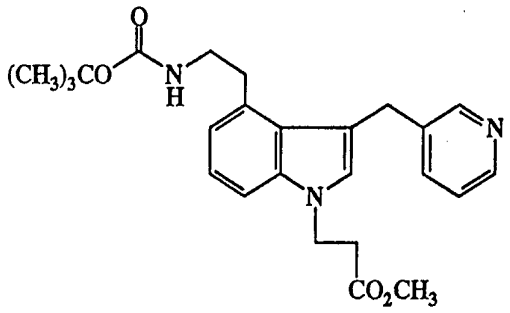
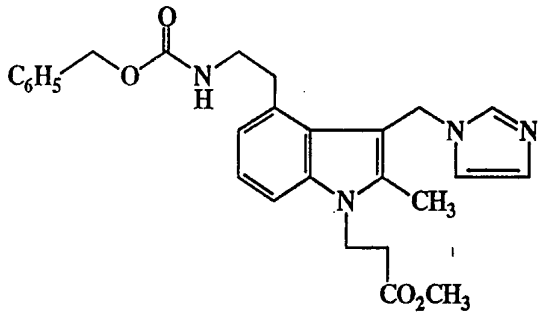
Treatment of benzyl 1-(2-methoxycarbonylethyl)-2-methyl-3-(3-pyridylmethyl)-1H-indole-1-propanoate (6.45g) with palladium on carbon (0.65g) and ammonium formate (8.90g) according to the method of Preparation 26 gave the title compound (3.76g). m.p. 165-167°C. Found: C,69.43; H,6.42; N,7.37. $C_{22}H_{24}N_2O_4$ requires: C,69.45; H,6.36; N,7.37%.

PREPARATION 28

Methyl 5-(2-benzyloxycarbonylaminoethyl)-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-1-propanoate

Diphenylphosphoryl azide (0.744g) was added to a mixture of methyl 5-(2-carboxyethyl)-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-1-propanoate (1.0g) and triethylamine (0.274g) in dry dioxan (5ml) at 50°C. The solution was then heated at 100°C for 1 hour to give a clear solution. Benzyl alcohol (0.352g) was added and the solution was heated at 100°C for a further 20 hours and then evaporated. The residue was partitioned between ethyl acetate and sodium bicarbonate solution. The organic layer was separated, washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel using dichloromethane/methanol (97:3) as eluent. The product fractions were combined and evaporated to give the title compound as a gum (0.41g). Found: C,68.12; H,6.41; N,11.23. $C_{27}H_{30}N_4O_4$ requires: C,68.33; H,6.37; N,11.81%.

The following compounds were prepared similarly using either benzyl alcohol or t-butanol.

Structure	m.p.°C	Analytical Data
	Gum	Rf. 0.4(SS4). δ ($CDCl_3$): 1.46(9H,s), 2.82(2H,t), 2.89(2H,t), 3.42(2H,m), 3.67(3H,s), 4.08(2H,s), 4.41(2H,t), 4.58(1H,br), 6.84(1H,s), 7.08(1H,d), 7.22(1H,m), 7.28-7.32(2H,m), 7.55(1H,d), 8.47(1H,d), 8.59(1H,s).
	Gum	Rf. 0.5(SS3). δ ($CDCl_3$): 1.44(9H,s), 2.80(2H,t), 2.99(2H,t), 3.32(2H,m), 2.65(3H,s), 4.15(2H,s), 4.38(2H,t), 4.57(1H,br), 6.75(1H,s), 6.87(1H,d), 7.16-7.22(3H,m), 7.45(1H,d), 8.44(1H,d), 8.50(1H,s).
	127.5-129.5	Found: C,68.15; H,6.42; N,11.77. $C_{27}H_{30}N_4O_4$ requires: C,68.33; H,6.37; N,11.81%.

PREPARATION 29

Methyl 5-(2-t-butoxycarbonylaminoethyl)-2-methyl-3-(3-pyridylmethyl)-1H-indole-1-propanoate

Diphenylphosphoryl azide (3.99g) was added to a stirred mixture of methyl 5-(2-carboxyethyl)-2-methyl-3-(3-pyridylmethyl)-1H-indole-1-propanoate (5.00g) and triethylamine (1.46g) in dry t-butanol (30ml) and the mixture was heated at 100°C for 18 hours and then evaporated. The residue was dissolved in dichloromethane, and the solution was washed twice with water and dried ($MgSO_4$). The solvent was evaporated and the residue was chromatographed on silica gel. Elution with dichloromethane and evaporation of the product fractions gave the title compound as a gum (4.51g), Rf. 0.35(SS4).

δ ($CDCl_3$): 1.42(9H,s), 2.37(3H,s), 2.73(2H,t), 2.82(2H,t), 3.36(2H,m), 3.68(3H,s), 4.05(2H,s), 4.39(2H,t), 4.50(1H,br), 7.00(1H,d), 7.10-7.25(3H,m), 7.41(1H,d), 8.39(1H,d), 8.50(1H,s).

PREPARATION 30

Methyl 4-(2-t-butoxycarbonylaminoethyl)-2-methyl-3-(3-pyridylmethyl)-1H-indole-1-propanoate

Treatment of methyl 4-(2-carboxyethyl)-2-methyl-3-(3-pyridylmethyl)-1H-indole-1-propanoate (3.70g) with diphenylphosphoryl azide (2.95g), triethylamine (1.08g), and t-butanol (30ml) as described in Preparation 29 gave the title compound as an oil (3.46g), Rf. 0.5 (SS2).

δ ($CDCl_3$): 1.44(9H,s), 2.37(3H,s), 2.77(2H,t), 2.87(2H,t), 3.23(2H,m), 3.68(3H,s), 4.28(2H,s), 4.45(2H,t), 4.53(1H,br), 6.82(1H,d), 7.10-7.13(2H,m), 7.21(1H,d), 7.29(1H,d), 8.38-8.42(2H,m).

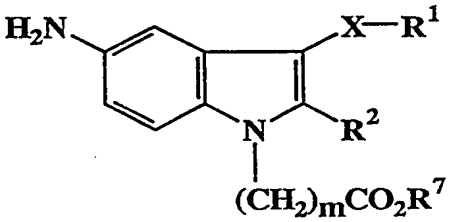
PREPARATION 31

Methyl 5-amino-3-(3-pyridylmethyl)-1H-indole-1-propanoate

A mixture of methyl 5-nitro-3-(3-pyridylmethyl)-1H-indole-1-propanoate (1.20g) and 10% palladium on carbon (120mg) in methanol (75ml) was hydrogenated at 50°C and 4.5 atm. until reduction was complete (2 hours). The mixture was filtered and the catalyst was washed well with methanol. The filtrate and washings were combined and evaporated to give the title compound as an oil (1.05g), Rf. 0.2(SS2).

δ ($CDCl_3$): 2.76(2H,t), 3.45(2H,br), 3.63(3H,s), 3.98(2H,s), 4.32(2H,t), 6.65-6.68(1H,dd), 6.72(1H,d), 6.77(1H,s), 7.11(1H,d), 7.14-7.18(1H,m), 7.48-7.51(1H,m), 8.42-8.44(1H,m), 8.56(1H,d).

The following compounds were prepared similarly as oils.



R^1	X	R^2	m	R^7	Analytical Data
1-imidazolyl	CH_2	H	2	CH_3	Rf. 0.7(SS5). δ ($CDCl_3$): 2.83(2H,t), 3.47(2H,br), 3.67(3H,s), 4.38(2H,t), 5.19(2H,s), 6.68(1H,d), 6.71-6.74 (1H,dd), 6.96(1H,s), 7.06(1H+1H,s), 7.15(1H,d), 7.59(1H,s).
1-imidazolyl	CH_2	CH_3	2	CH_3	Rf. 0.4(SS2). δ ($CDCl_3$): 2.42(3H,s), 2.77(2H,t), 3.50(2H,br), 3.68(3H,s), 4.39(2H,t), 5.16(2H,s), 6.63-6.69(2H,m), 6.93(1H,s), 7.05(1H,s), 7.14(1H,d), 7.54(1H,s).
4-fluorophenyl	CH_2	H	2	CH_3	Rf. 0.4(SS6). δ ($CDCl_3$): 2.77(2H,t), 3.42(2H,br), 3.65(1H,s), 3.97(1H,s), 4.33(2H,t), 6.67(1H,dd), 6.68-6.69(2H,d+s), 6.95(2H,t), 7.12(1H,d), 7.17-7.22(2H,m).
3-pyridyl	direct link	H	2	CH_3	Rf. 0.2(SS2). δ ($CDCl_3$): 2.85(2H,t), 3.65(2H,br), 3.67(3H,s), 4.44(2H,t), 6.75(1H,dd), 7.18(1H,d), 7.27(1H,s), 7.27(1H,d), 7.30-7.34(1H,m), 7.87(1H,m), 8.47(1H,dd), 8.86(d).
3-pyridyl	direct link	H	3	C_2H_5	Rf. 0.2(SS2). δ ($CDCl_3$): 1.24(3H,t), 2.15(2H,m), 2.32(2H,t), 3.45(2H,br), 4.11(2H,t), 4.19(2H,t), 7.18-7.23 (3H,m), 7.30-7.35(1H,m), 7.89(1H,m), 8.47(1H,dd), 8.86(1H,dd).
H	direct link	H	2	CH_3	Rf. 0.25(SS6). δ ($CDCl_3$): 2.80(2H,t), 3.35(2H,br), 3.67 (2H,s), 4.39(2H,t), 6.30(1H,d), 6.68(1H,dd), 6.93(1H,d), 7.04(1H,d), 7.14(1H,d).

PREPARATION 32

Methyl 5-(2-aminoethyl)-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-1-propanoate

A solution of methyl 5-(2-benzyloxycarbonylaminoethyl)-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-1-propanoate (0.57g) in tetrahydrofuran (50ml) was hydrogenated at room temperature and 4.5 atm. pressure in the presence 10% palladium on carbon (50mg) for 20 hours. The mixture was filtered and the residue was washed with methanol. The filtrate and washings were combined and evaporated to give a gum which was chromatographed on silica gel. Elution with dichloromethane/methanol (19:1) gave impurity, and then further elution with dichloromethane/methanol/0.880 ammonia solution (95:5:1) gave pure product. The product fractions were evaporated to give the title compound as a gum (0.325g), Rf. 0.4 (SS3). The product was used directly for further reaction.

PREPARATION 33

Methyl 4-(2-aminoethyl)-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-1-propanoate

Hydrogenation of methyl 4-(2-benzyloxycarbonylaminoethyl)-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-1-propanoate (0.50g) in tetrahydrofuran (20ml) in the presence of 10% palladium on carbon (100mg + a further 50mg quantities after 24 and 48 hours) for 72 hours, followed by work up as described for Preparation 32 gave the title compound as a gum (0.20g), Rf. 0.15(SS3).

δ ($CDCl_3$): 1.70(2H,br), 2.47(3H,s), 2.81(2H,t), 2.88(4H,s), 3.70(3H,s), 4.48(2H,t), 5.37(2H,s), 6.86(1H,s), 6.95(1H,d), 7.04(1H,s), 7.17(1H,m), 7.24(1H,d), 7.42(1H,s).

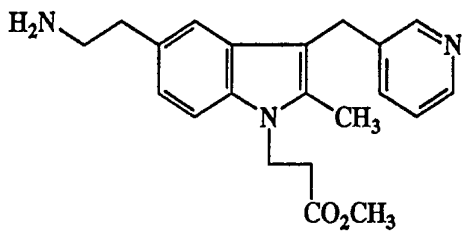
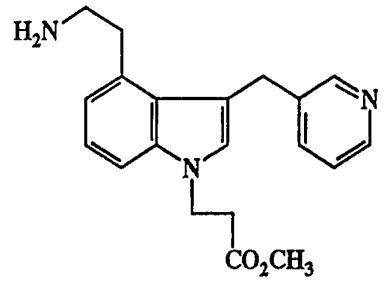
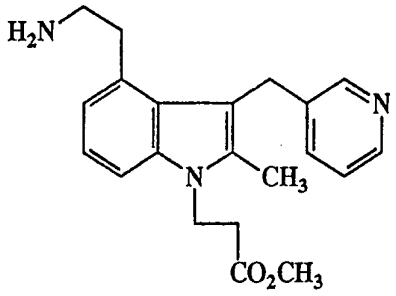
PREPARATION 34

Methyl 5-(2-aminoethyl)-3-(3-pyridylmethyl)-1H-indole-1-propanoate

Trifluoroacetic acid (5ml) was added to a stirred solution of methyl 5-(2-t-butoxycarbonylaminoethyl)-3-(3-pyridylmethyl)-1H-indole-1-propanoate (5.0g) in dry dichloromethane (50ml) and the solution was stirred for 3 hours. An additional 5ml of trifluoroacetic acid was then added and stirring was continued for a further 2 hours. The solution was evaporated and the residue was partitioned between dichloromethane and dilute aqueous ammonia. The aqueous layer was separated and extracted with dichloromethane. The organic layers were combined and evaporated. Water (ca 50ml) was added followed by sufficient acetic acid to adjust the pH to ca4. The solution was washed twice with ethyl acetate and then made basic with concentrated aqueous ammonia solution. The mixture was extracted twice with dichloromethane and the combined extracts were dried ($MgSO_4$) and evaporated to give the title compound as a gum (2.51g), Rf. 0.15 (SS3).

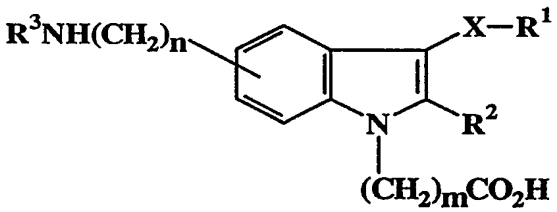
δ ($CDCl_3$): 1.39(2H,s), 2.80-2.86(4H,m), 2.98(2H,t), 3.67(3H,s), 4.08(2H,s), 4.42(2H,t), 6.83(1H,s), 7.08(1H,d), 7.20(1H,m), 7.27-7.29(2H,m), 7.54(1H,d), 8.45(1H,d), 8.59(1H,s).

The following compounds were prepared similarly.

Structure	Analytical Data
	Rf. 0.4(SS5). δ ($CDCl_3$): 1.47(2H,s), 2.38(3H,s), 2.71-2.80(4H,m), 2.92(2H,t), 3.66(3H,s), 4.04(2H,s), 4.40(2H,t), 7.00(1H,d), 7.11(1H,m), 7.18(1H,s), 7.22(1H,d), 7.40(1H,d), 8.36(1H,d), 8.52(1H,s).
	Rf. 0.45(SS3). δ ($CDCl_3$): 1.08(2H,br), 2.77(2H,t), 2.88-2.97(4H,m), 3.65(3H,s), 4.22(2H,s), 4.35(2H,t), 6.69(1H,s), 6.87(1H,d), 7.12-7.26(3H,m), 7.45(1H,d), 8.45(1H,d), 8.51(1H,s).
	Rf. 0.4(SS3). δ ($CDCl_3$): 2.37(3H,s), 2.76(2H,t), 2.85(2H,t), 2.97(2H,t), 3.68(3H,s), 4.21(2H,s), 4.30(2H,br), 4.44(2H,t), 6.82(1H,d), 7.05-7.11(2H,m), 7.20(1H,d), 7.24-7.26(1H,m), 8.31(1H,d), 8.45(1H,s).

CLAIMS

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt or biolabile ester thereof, wherein R^1 is H, C_1-C_4 alkyl, phenyl optionally substituted by up to three substituents independently selected from C_1-C_4 alkyl, phenyl optionally substituted by up to three substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and CF_3, or is 1-imidazolyl, 3-pyridyl or 4-pyridyl,
R^2 is H or C_1-C_4 alkyl,
R^3 is SO_2R^4 or COR^4 where R^4 is C_1-C_6 alkyl, C_1-C_3 perfluoroalkyl$(CH_2)_p$, C_3-C_6 cycloalkyl$(CH_2)_p$, aryl$(CH_2)_p$ or heteroaryl$(CH_2)_p$, p being 0, 1 or 2, or R^4 may be NR^5R^6 where R^5 is H or C_1-C_4 alkyl and R^6 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl or aryl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a 5- to 7-membered heterocyclic ring which may optionally incorporate a carbon-carbon double bond or a further heteroatom linkage selected from O, S, NH, N(C_1-C_4 alkyl) and N(C_1-C_5 alkanoyl);
X is CH_2 or a direct link, with the proviso that when R^1 is 1-imidazolyl then X is CH_2;
m is 2, or 3
n is 0, 1 or 2
and wherein the group $(CH_2)_nNHR^3$ is attached at the 5-position when n is 0 or 1, or at the 5- or 4-position when n is 2.

2. A compound, pharmaceutically acceptable salt or biolabile ester, according to claim 1, where R^1 is optionally substituted phenyl or pyridyl, R^2 is H, R^3 is SO_2R^4 where R^4 is optionally substituted phenyl, X is CH_2, m is 2, n is 0 or 2, and $(CH_2)_nNHR^3$ is attached at the 5-position.

3. A compound, pharmaceutically acceptable salt or biolabile ester, according to claim 1, where R^1 is pyridyl, R^2 is H, R^3 is SO_2R^4 where R^4 is optionally substituted phenyl or, R^3 is COR^4 where R^4 is alkyl, X is CH_2, m is 2, n is 2 and $(CH_2)_nNHR^3$ is attached at the 4-position.

4. A compound, pharmaceutically acceptable salt or biolabile ester, according to claim 1, where R^1 is 4-fluorophenyl, R^3 is arylsulphonyl, X is CH_2, m is 2, n is 0 and $(CH_2)_nNHR^3$ is attached at the 5-position, or wherein R^1 is pyridyl, R^3 is 3-methylbutanoyl, X is CH_2, m is 2, n is 2 and $(CH_2)_nNHR^3$ is attached at the 4-position.

5. Any one of the following compounds, or pharmaceutically acceptable salts thereof:

(i) methyl 5-[2-(4-fluorophenylsulphonyl)amino)ethyl]-3-(3-pyridylmethyl)-1H-indole-1-propanoate;

(ii) methyl 5-((4-fluorophenylsulphonyl)amino)-3-(1H-imidazol-1-ylmethyl)-1H-indole-1-propanoate;

(iii) methyl 5-((4-fluorophenylsulphonyl)amino)-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-1-propanoate;

(iv) methyl 5-((4-fluorophenylsulphonyl)amino)-3-(4-fluorophenylmethyl)-1H-indole-1-propanoate;

(v) methyl 5-((4-chlorophenylsulphonyl)amino)-3-(4-fluorophenylmethyl)-1H-indole-1-propanoate;

(vi) methyl 5-((4-chlorophenylsulphonyl)amino)-3-(3-pyridyl)-1H-indole-1-propanoate;

(vii) ethyl 5-((4-chlorophenylsulphonyl)amino)-3-(3-pyridyl)-1H-indole-1-butanoate;

(viii) methyl 5-((4-fluorophenylsulphonyl)amino)-3-(3-pyridylmethyl)-1H-indole-1-propanoate;

(ix) methyl 5-((4-fluorophenylsulphonyl)amino)-3-(3-pyridylmethyl)-1H-indole-1-butanoate;

(x) methyl 5-[2-((4-fluorophenylsulphonyl)amino)ethyl]-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-propanoate;

(xi) methyl 4-[2-((4-fluorophenylsulphonyl)amino)ethyl]-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-propanoate;

(xii) methyl 5-[2-((4-fluorophenylsulphonyl)amino)ethyl]-3-(3-pyridylmethyl)-1H-indole-propanoate;

(xiii) methyl 5-[2-(dimethylaminosulphonyl)amino)ethyl]-3-(3-pyridylmethyl)-1H-indole-propanoate;

(xiv) methyl 5-[2-(3-methylbutanoylamino)ethyl]-3-(3-pyridylmethyl)-1H-indole-propanoate;

(xv) methyl 4-[2-((4-fluorophenylsulphonyl)amino)ethyl]-3-(3-pyridylmethyl)-1H-indole-propanoate;

(xvi) methyl 4-[2-((dimethylaminosulphonyl)amino)ethyl]-(3-pyridylmethyl)-1H-indole-propanoate;

(xvii) methyl 4-[2-((3-methylbutanoyl)amino)ethyl]-3-(3-pyridylmethyl)-1H-indole-propanoate;

(xviii) methyl 5-[2-((4-fluorophenylsulphonyl)amino)ethyl]-3-(3-pyridylmethyl))-2-methyl-1H-indole-propanoate;

(xix) methyl 5-[2-((4-iodophenylsulphonyl)amino)ethyl]-3-(3-pyridylmethyl)-2-methyl-1H-indole-propanoate;

(xx) methyl 5-[2-((4-trifluoromethylphenylsulphonyl)amino)-3-(3-pyridylmethyl)-2-methyl-1H-indole-propanoate;

(xxi) methyl 4-[2-((4-fluorophenylsulphonyl)amino)ethyl]-3-(3-pyridylmethyl)-2-methyl-1H-indole-propanoate;

(xxii) methyl 5-[4-chlorophenylsulphonyl)amino]-1H-indole-propanoate;

(xxiii) methyl 5-[4-fluorophenylsulphonyl)amino]-1H-indole-propanoate;

(xxiv) methyl 5-[(phenylsulphonyl)amino]-3-[(4-fluorophenyl)methyl]-1H-indole-propanoate;

(xxv) methyl 3-[(4-fluorophenyl)methyl]-5-[(4-trifuoromethylphenyl-sulphonyl)amino]-1H-indole-propanoate;

(xxvi) methyl 3-[(4-fluorophenyl)methyl]-5-[(4-methoxyphenyl-sulphonyl)amino]-1H-indole-propanoate;

(xxvii) methyl 3-[(4-fluorophenyl)methyl]-5-[(4-methylphenysulphonyl)amino]-1-H-indole propanoate.

(xxviii) methyl 5-[[(2-cyclopropyl)acetyl]amino]ethyl-3-(3-pyridylmethyl))-1H-indole-1-propanoate;

(xxix) 5-[(4-Fluorophenyl)sulphonyl]amino-3-(3-pyridylmethyl)-1H-indole-1-propanoic acid;

(xxx) 5-[(4-fluorophenylsulphonyl)amino]-3-(1H-imidazol-1-ylmethyl)-1H-indole-1-propanoic acid;

(xxxi) 5-[(4-fluorophenylsulphonyl)amino]-3-(1H-imidazol-1-ylmethyl)-2-methyl -1H-indole-1-propanoic acid;

(xxxii) 5-[(4-fluorophenylsulphonyl)amino]-3-(4-fluorophenylmethyl)-1H-indole-1-propanoic acid;

(xxxiii) 5-[(4-chlorophenylsulphonyl)amino]-3-(4-fluorophenylmethyl)-1H-indole-1-propanoic acid;

(xxxiv) 5-[(4-chlorophenylsulphonyl)amino]-3-(3-pyridyl)-1H-indole-1-propanoic acid;

(xxxv) 5-[(4-chlorophenylsulphonyl)amino]-3-(3-pyridyl)-1H-indole-1-butanoic acid;

(xxxvi) 5-[(4-fluorophenylsulphonyl)amino]-3-(3-pyridylmethyl)-1H-indole-1-butanoic acid;

(xxxvii) 5-[2-((4-fluorophenylsulphonyl)amino)ethyl]-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-1-propanoic acid;

(xxxviii) 4-[2-((4-fluorophenylsulphonyl)amino)ethyl]-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-1-propanoic acid;

(xxxix) 5-[2-((4-fluorophenylsulphonyl)amino)ethyl]-3-(3-pyridylmethyl)-1H-indole-1-propanoic acid;

(xl) 5-[2-((methylsulphonyl)amino)ethyl]-3-(3-pyridylmethyl)-1H-indole-1-propanoic acid;

(xli) 5-[2-((dimethylaminosulphonyl)amino)]-3-(3-pyridylmethyl)-1H-indole-1-propanoic acid;

(xlii) 5-[2-((3-methylbutanoyl)amino)ethyl]-3-(3-pyridylmethyl)-1H-indole-1-propanoic acid;

(xliii) 5-[2-((cyclopropylacetyl)amino)ethyl]-3-(3-pyridylmethyl)-1H-indole-1-propanoic acid;

(xliv) 4-[2-((4-fluorophenylsulphonyl)amino)ethyl]-3-(3-pyridylmethyl)-1H-indole-1-propanoic acid;

(xlv) 5-[2-((dimethylaminosulphonyl)amino)ethyl]-3-(3-pyridylmethyl)-1H-indole-1-propanoic acid;

(xlvi) 5-[2-((3-methylbutanoyl)amino)ethyl]-3-(3-pyridylmethyl)-1H-indole-1-propanoic acid;

(xlvii) 5-[2-((4-fluorophenylsulphonyl)amino)ethyl]-3-(3-pyridylmethyl)-2-methyl-1H-indole-1-propanoic acid;

(xlviii) 5-[2-((4-iodophenylsulphonyl)amino)ethyl]-3-(3-pyridylmethyl)-2-methyl-1H-indole-1-propanoic acid;

(il) 5-[2-((4-trifluoromethylphenylsulphonyl)amino)ethyl]-3-(3-pyridylmethyl)-2-methyl-1H-indole-1-propanoic acid;

(l) 4-[2-((4-fluorophenylsulphonyl)amino)ethyl]-3-(3-pyridylmethyl)-2-methyl-1H-indole-1-propanoic acid;

(li) 5-[(4-chlorophenylsulphonyl)amino]-1H-indole-1-propanoic acid;

(lii) 5-[(4-fluorophenylsulphonyl)amino]-1H-indole-1-propanoic acid;

(liii) 3-(4-fluorophenyl)methyl-5[(phenylsulphonyl)amino]-1H-indole-1-propanoic acid;

(liv) 3-(4-fluorophenyl)methyl-5-[(4-trifluoromethylphenylsulphonyl)amino]-1H-indole-1-propanoic acid;

(lv) 3-(4-fluorophenyl)methyl-5[(4-methoxyphenylsulphonyl)amino]-1H-indole-1-propanoic acid;

(lvi) 3-(4-fluorophenyl)methyl-5-[(4-methylphenylsulphonyl)amino]-1H-indole-1-propanoic acid;

(lvii) 5-[(4-fluorophenyl)sulphonyl]amino-2,3-dimethyl-1H-indole-1-propanoic acid

6. A compound, salt or ester according to any of the preceding claims, which is radiolabelled.

7. A compound, salt or ester according to any of claims 1 to 5, for use in a medicament.

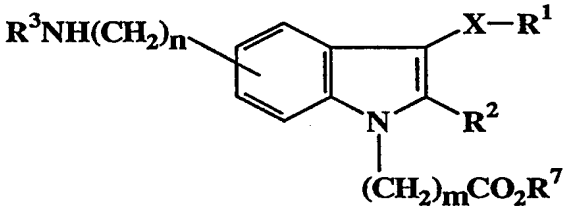
8. A compound, salt or ester according to any of claims 1 to 5, for use in the manufacture of a pharmaceutical or veterinary composition.

9. A pharmaceutical or veterinary composition comprising a compound, salt ot ester according to any of claims 1 to 5, and a thromboxane A_2 synthase inhibitor.

10. A compound, salt or ester, according to any of claims 1 to 5, for making a medicament useful in the treatment or prophylaxis of diseases or disorders mediated by thromboxane A_2 or prostaglandin H_2.

11. A method of treatment or prophylaxis of diseases or disorders mediated by thromboxane A2 or prostaglandin H_2, which comprises administering to an animal or human an effective amount of a compound, salt or ester according to any of claims 1 to 5.

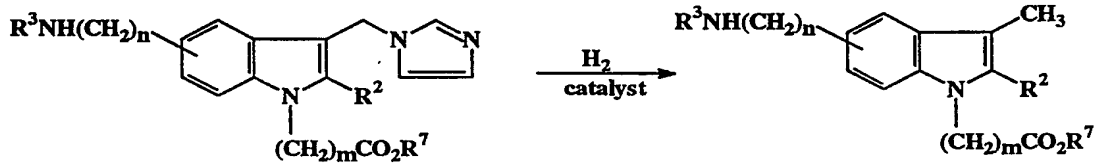
12. A process whereby compounds of formula (I) are obtained by hydrolysis of their lower alkyl ester precursors of formula (II):



(II)

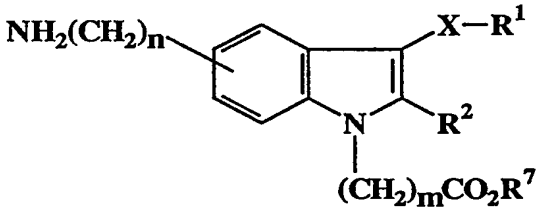
wherein R^1,R^2,R^3,m,n,p and X are as defined in Claim 1 and R^7 is C_1-C_4 alkyl.

13. A process for obtaining compounds of formula (I), where R^1=H and X=CH_2, comprising catalytic hydrogenation of compounds of formula (I) where R^1=1-imidazolyl and X=CH_2,



wherein R^2,R^3, and R^7 are as defined above.

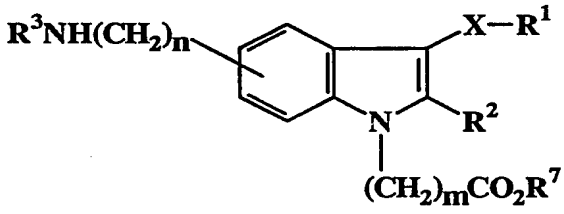
14. A process for obtaining compounds of formula (II) where R^3 is SO_2R^4 or COR^4 comprising sulphonation/sulphamoylation or acylation, respectively of an amine of formula (III):



(III)

wherein R^1, R^2, R^3, R^4, R^7, X, m and n are as defined above.

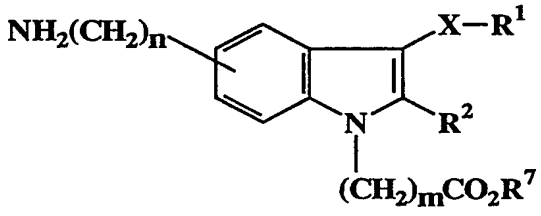
15. A compound of formula (II):-



(II)

wherein R^1, R^2, R^3, m, n, p and X are as defined in Claim 1 and R^7 is C_1-C_4 alkyl.

16. A compound of formula (III)



(III)

wherein R^1, R^2, R^3, R^4, R^7, X, m and n are as defined above.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 94/02660

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/06 A61K31/405 C07D209/10 C07D401/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB,A,2 045 244 (PFIZER LTD.) 29 October 1980 see claims	1,10
A	EP,A,0 073 663 (PFIZER LTD.) 9 March 1983 see claims	1,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 1994	19. 10. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 94/02660

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 11 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ ~~As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.~~

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intc onal Application No
PCT/EP 94/02660

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A-2045244	29-10-80	AT-B-	375366	25-07-84
		AT-B-	375932	25-09-84
		AU-B-	516957	02-07-81
		AU-A-	5623180	11-09-80
		BE-A-	882113	08-09-80
		CA-A-	1120479	23-03-82
		CH-A-	649546	31-05-85
		DE-A,C	3008632	16-10-80
		FR-A,B	2450832	03-10-80
		LU-A-	82224	06-06-80
		NL-A-	8001351	09-09-80
		SE-B-	440778	19-08-85
		SE-A-	8001736	08-09-80
		SU-A-	1277894	15-12-86
		US-A-	4273782	16-06-81
EP-A-0073663	09-03-83	AU-A-	8759982	24-03-83
		CA-A-	1178964	04-12-84
		SU-A-	1217256	07-03-86
		SU-A-	1194278	23-11-85
		US-A-	4496572	29-01-85
		US-A-	4590200	20-05-86